Medical Lib

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

Vol. XXXII—No. 363] BALTIMORE, MAY, 1921 [Price, 50 Cents

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Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

EPIDEMIC ENCEPHALITIS

A CLINICAL STUDY

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The recent epidemic of encephalitis began in Europe during the winter of 1916-1917 and the first cases were reported by von Economo[1] from Austria and by Cruchet[2] from Northern France at about the same time. Early the next winter the disease appeared in epidemic form in Paris where it was studied by Netter[3] and others.[4, 5] Following these publications instances of the disease were recognized in many localities throughout Europe. The first cases observed in England were mistaken for botulism,[6, 7] but the error was soon corrected and the identity of the British and continental cases was established as the result of the investigations of McNalty, James, Marinesco and McIntosh,[8] and others.[9, 10]

The malady did not remain confined to Europe, but probably favored in its spread by extensive troop movements, soon appeared in Africa, Asia, Australasia and America.[11, 12] It was apparent, therefore, that the various local epidemics were in reality parts of a great pandemic of a disease of the nervous system.

Since the appearance of the epidemic in the United States during the winter of 1918-1919 we have had an opportunity to observe a large number of patients affected with the disease in the wards of The Johns Hopkins Hospital, and in many instances it has been possible to follow them for a considerable period of time after their discharge. We believe, therefore, that a presentation of the chief clinical features and of the late symptoms and sequelæ of the disease in this series of cases may be of interest at this time.

Nomenclature

The disease, originally described under the headings "Encephalitis lethargica" by von Economo[1] and "Diffuse Encephalomyelitis" by Cruchet[2] in 1917, has recently been given a number of different names, such as Encephalitis myoclonica,[13, 14] Encephalitis choreiformis[15] and Encephalitis comatosa, depending on the predominant clinical symptoms presented by the patient. The tendency to diversity of nomenclature is unfortunate, because the numerous types of the disease so merge one into another that no one name based on the clinical features is applicable to a large number of cases. Thus, Bourges and Marcandier[16] reported an instance of the disease in which choreiform, myoclonic, catatonic, lethargic, athetotic, delirious and comatose stages were observed successively.

Moreover, it is incorrect to combine the term "encephalitis" indicating a pathological process with the descriptive term "lethargica," "choreatica," etc. It would be more logical and more convenient, therefore, to include all cases

of the disease under the heading "Epidemic Encephalitis" and, if necessary for descriptive purposes, to add the modifying phrase "with lethargy," "with myoclonia," etc.

The name "Epidemic Encephalitis" was first employed by Buzzard[17] in 1918 and has lately received wide usage. It is open to two objections which, however, are not serious. In the first place, the lesions in many instances are not limited to the encephalon but may be present in the meninges, spinal cord and peripheral nerves, and it would be more correct to employ the more comprehensive term "meningo-encephalomyelo-neuritis" in some instances, as proposed by Barker, Cross and Irwin.[18] Unfortunately this designation is too cumbersome for popular usage. In the second place, the term "epidemic" is not applicable to sporadic cases, as Netter has pointed out. Despite these minor objections, the name "Epidemic Encephalitis" will be employed throughout this paper as the most suitable designation so far proposed.

Epidemiology

It is of particular interest that the pandemic of encephalitis occurred almost simultaneously with a pandemic of severe influenza and, as was to be expected, the causal and epidemiological relationship of the two maladies was carefully investigated by a large number of epidemiologists and medical historians. Crookshank[19] concluded, from a study of the historical features of encephalitis and influenza, that epidemics and endemics of a disease similar to the epidemic encephalitis of recent years have been observed for at least four centuries. In great part they have appeared shortly before or after or in geographical proximity to epidemics known variously as "influenza," "la grippe," or "sweating sickness."

The simultaneous occurrence of the two great pandemics in recent years is, therefore, not especially remarkable, for as pointed out above, the two diseases have often occurred in close temporal relationship. Furthermore, although the two pandemics appeared at about the same time, they seem to have been disseminated by somewhat different paths, so that in one part of the world encephalitis preceded influenza, in another influenza preceded encephalitis and in other localities the two occurred simultaneously. Epidemiological investigations of the diseases, therefore, lend little support to the conception of certain authors that epidemic encephalitis is a post-influenzal affection. Moreover, we have as yet no methods of differentiating influenza from certain other acute infections or epidemic encephalitis from similar cases of acute or sub-acute non-suppurative encephalomyelitis. Ophthalmological[20] as well as neurological[21] literature prior to the recent epidemic contains records of cases similar to if not identical both clinically and histopathologically with epidemic encephalitis. A number of these have occurred sporadically. It is probable, therefore, that influenza and epidemic encephalitis frequently occur in sporadic form and that, in consequence, epidemics of either or both of these diseases are possible when conditions at present not well understood are favorable to their wide dissemination.

A study of the records of our cases of epidemic encephalitis has shown that influenza in a recognizable form has seldom preceded directly the onset of encephalitis. In a number of instances, moreover, the patients were born after the major epidemic of influenza. The evidence at hand, therefore, does not favor the assumption that the two diseases are causally related, but since our knowledge of the etiology of each affection is still incomplete, a certain solution of the problem is not possible.

Epidemic encephalitis, although in all probability an infectious disease, is only slightly contagious. It is remarkable that the affection became world-wide in distribution with so few evidences of its direct transmission. Netter could find but eight cases in France and an equal number reported from England in which the disease occurred in more than one member of a family. Although a large number of patients with the disease have been cared for in hospitals, reported instances of bed to bed or even of ward infection are rare. An outbreak in an institution for girls has been reported[8]—the only instance of the kind we have encountered in the literature. Guillain and Lechelle[24] reported a case of the disease which occurred between 15 and 30 days after the patient had visited the home of his father who had died of the disease seven months previously. Roger,[25] in a recent article, stated that, although about 10,000 cases of encephalitis had occurred in France, direct contagion could be traced in only 174 cases. In no locality had a true epidemic occurred. He believed that the disease was transmitted by means of healthy carriers or unrecognized cases.

James,[22] Netter,[23] and Bernard and Renault,[26] studied the epidemiology of a large number of cases in France and in England and concluded that, although widely distributed, the disease occurred chiefly in the more thickly populated districts. The precise mode of dissemination could not be determined from their studies.

In our series of 81 cases we have not encountered a single instance in which more than one member of a family or household was affected, nor has it been possible to determine the mode of infection.

The accompanying chart (Table I) shows the age, sex and color of the patients and also the date of the onset of symptoms. It will be seen that there were 46 males and 35 females. The ages varied from seven weeks to 65 years. Over half of the patients were past the tenth year. The chart shows furthermore that the greatest number of cases developed during the months of January, February and March, although cases appeared throughout the entire year.

Clinical Considerations

It will be convenient to preface the discussion of the symptomatology of epidemic encephalitis by some important inferences which may be drawn from the histopathological studies of the disease.

The wide distribution of the lesions of the nervous system which may be surmised from clinical examination during the course of the affection readily explains the multiplicity and

TABLE I

(THE CASE NUMBER REFERS TO CASES CITED IN THE TEXT)

Case No.	Age	Sex	Color	Date of onset of symptoms	Cerebrospinal fluid				
					Day of disease	Number of cells	Wassermann reaction	Globulin	Gold chloride curve
1	4 years.	M.	W.	January 16, 1920.	90±	10	Negative.	0	0000000000
					102±	3	.....	0	1000000000
					160±	5	.....	0	0000000000
2	11 years.	M.	W.	February 19, 1920.	3	7	Negative.	0	
					6	28	.....	0	
					23	5	.....	+	
					45	2	.....	+	
					65	1	.....	+	1111000000
3	12 years.	M.	W.	October, 1919.	8	10	Negative.	0	0001000000
4	16 years.	F.	W.	November, 1919.					
5	6 years.	F.	W.	November 9, 1919.	4	4	Negative.	+	1121000000
					11	3			
6	65 years.	M.	W.	August, 1919.	60±	200	Negative.	0	0011000000
					62±	90	.....	0	
					77±	40	.....	0	
7	24 years.	M.	W.	January, 1920.	19	30	Negative.	+	Negative.
					43	17	Negative.	+	Atypical paretic.
8	37 years.	M.	W.	February, 1920.	120	70	Negative.	0	1122210000
9	6 years.	F.	W.	September 16, 1920.	4	14	Negative.	+	
					8	26		+	
10	24 years.	F.	W.	February, 1919.	20	17	Negative.	++	2244211000
11	36 years.	M.	W.	March, 1920.	23	19	Negative.	++	Luetic zone.
					26	44	.....	++	Luetic zone.
					49	3	.....	+	Luetic zone.
					65	1	.....	+	Luetic zone.
12	35 years.	M.	B.	March, 1920.	42	6	Negative.	+	2222200000
13	5 years.	M.	W.	February 4, 1920.	5	55	Negative.	+	1111221000
14	8 years.	M.	W.	May 18, 1920.	1	50	Negative.	+	
					2	40	Negative.	+	1111110000
					3	250	.....	+	
					9	66	.....	+	
					16	11	.....	+	
15	18 months.	F.	W.	September 26, 1920.	4	33	Negative.	0	
16	34 years.	M.	W.	December, 1920.	14	26	Negative.	0	0000000000
17	7 weeks.	F.	W.	April 1, 1919.	5	28	Negative.	+	1122210000
					10	10	.....	0	
18	28 years.	F.	B.	May, 1920.	5	9	Negative.	+	
19	19 years.	M.	B.	March, 1920.	4	368	Negative.	0	1444110000
20	2 months.	M.	W.	April 2, 1920.	4	56	Negative.	+	
					7	34	.....	+	
					12	22	.....	+	
					17	11	.....	+	
21	4 months.	F.	W.	March 17, 1920.	1	10	.....	0	
					9	20	Negative.	+	0110000000
					17	11	.....	+	
					28	8	.....	+	
22	5 years.	F.	W.	February 1, 1920.	49	6	Negative.	++	1222100000
23	10 years.	F.	W.	May 15, 1920.	75	28	.....	++	
					79	11	Negative.	+	2233443210
					86	6	Negative.	+	0112011100
					95	3	.....	+	
24	2 years.	M.	B.	August 8, 1920.	2	18	Negative.	0	
					4	21	.....	0	
					7	5	.....	0	
					16	3	.....	0	
25	37 years.	M.	W.	March, 1920.	21	70	Negative.	+	1222100000
26	25 years.	M.	W.	March, 1920.	120±	3	Negative.	0	0000000000
27	26 years.	M.	W.	June, 1920.	60+	15	Negative.	+	
28	3 years.	F.	W.	September 6, 1920.	6	7	Negative.	0	
					22	6	.....	0	

TABLE I—CONTINUED

Case No.	Age	Sex	Color	Date of onset of symptoms	Cerebrospinal fluid				
					Day of disease	Number of cells	Wassermann reaction	Globulin	Gold chloride curve
29	17 years.	F.	B.	February, 1920.	30	225	Negative.	+	1111000000
					35	20	Negative.	+	1111000000
30	27 years.	F.	B.	October, 1920.	5	3	Negative.	0	3442100000
31	42 years.	M.	W.	September, 1919.	30	22	Negative.	+	
32	25 years.	M.	W.	February, 1920.	7	25	Negative.	0	
					10	58	Negative.	0	
					40	4	Negative.	0	
33	3 years.	F.	W.	February, 1920.	120±	3	Negative.	0	1121100000
34	9 years.	M.	W.	February 27, 1920.	180±	Blood.	Negative.		
35	2 years.	M.	B.	March 1, 1920.	27	19	Negative.	+	1111000000
					31	26	.....	0	
					34	18	.....	0	
					45	26	.....	+	
					66	10	.....	+	
36	6 years.	M.	W.	February 3, 1920.	90	2	Negative.	+	
37	9 years.	F.	W.	April, 1920.					
38	7 years.	M.	W.	February 19, 1920.	5	36	Negative.	+	1110000000
39	9 years.	M.	W.	February 11, 1920.	8	51	Negative.	+	0110000000
40	29 years.	M.	W.	February, 1920.	?	8	Negative.	0	
41	13 years.	F.	B.	April, 1920.	59	60	Negative.	0	
42	1½ years.	M.	W.	September 20, 1920.	1	8	Negative.	+	
43	2½ months.	M.	W.	June 9, 1920.	6	36	Negative.	+	1111110000
44	5½ years.	F.	W.	May 6, 1920.	60	20	Negative.	+	1111100000
45	2 years.	F.	W.	October 2, 1918.	8	92	Negative.	0	
					17	9	.....	0	
46	2 years.	F.	W.	August, 25, 1919.	3	30	Negative.	0	
					6	12	.....	0	
47	20 years.	F.	W.	December, 1918.	11	42	Negative.	++	0122110000
					13	70	Negative.	+	1122100000
					16	74	Negative.	0	1143210000
					46	13	Negative.	+++	4555421000
					64	6	Negative.	+	5443210000
48	47 years.	F.	W.	February, 1919.	42	2	Negative.	+	Luetic zone.
					50	7	Negative.	+	Atypical paretic.
49	48 years.	M.	W.	February, 1919.	22	97	Negative.	+++	Meningitic curve.
					27	133	Negative.	++++	Paretic curve.
					52	50	Negative.	+++	Atypical.
					65	3	Negative.	+	
50	33 years.	F.	W.	March, 1919.	7	Blood.	Negative.		
51	32 years.	F.	W.	March, 1919.	60±	4	Negative.	0	0122100000
52	40 years.	M.	B.	July, 1919.	24	40	Negative.	++	2244210000
					38	7	Negative.	+	1223211000
53	37 years.	M.	W.	November, 1919.	35	30	Negative.	0	1121000000
					39	46	Negative.	0	1111100000
					55	10	Negative.	0	0111100000
54	7 years.	F.	W.	February 24, 1920.	120±	3	Negative.	+	0000000000
55	9 years.	M.	W.	January 6, 1920.	360±	38	Negative.	+	0001110000
					390±	6	.....	+	4223010000
56	3 years.	M.	W.	May 9, 1920.	7	3	Negative.	+	
					9	3	.....	0	
57	8 years.	F.	W.	January 16, 1920.	5	132	Negative.	+	
					7	72	.....	+	1122100000
					11	51	.....	+	
58	8 years.	M.	W.	June 2, 1919.	4	160	Negative.	0	
					6	250	.....	+	
					12	230	.....	0	
					17	8	.....	0	
59	5 years.	F.	W.	November 27, 1919.	7	27	Negative.	+	0111000000
					17	7	.....	+	

TABLE I—CONTINUED

Case No.	Age	Sex	Color	Date of onset of symptoms	Cerebrospinal fluid				
					Day of disease	Number of cells	Wassermann reaction	Globulin	Gold chloride curve
60	6 years.	F.	W.	June 18, 1919.	4	55	Negative.	0	
					5	56	.....	0	
61	25 years.	F.	B.	March, 1920.	?	3	Negative.	0	1111200000
62	44 years.	F.	W.	December, 1919.	300+	23	Negative.	+	Negative.
63	48 years.	M.	W.	February, 1920.	330+	5	Negative.	++	Luetic zone.
64	37 years.	M.	W.	December, 1920.	26	23	Negative.	+	0000000000
65	13 years.	F.	W.	December, 1920.	42	3	Negative.	0	
66	19 years.	F.	B.	January, 1920.					
67	20 years.	F.	B.	January, 1920.	60	25	Negative.	+	4411100000
					100	10	Negative.	..	2443311000
68	26 years.	M.	B.	February, 1920.	21	150	Negative.	+	1121000000
					27	150	Negative.	+	2221100000
					37	60	Negative.	0	1222100000
					67	1	Negative.	0	
69	34 years.	M.	B.	February, 1920,	42±	30	Negative.	+	1343210000
					72±	20	.....		
70	43 years.	M.	B.	March, 1920.	22	87	Negative.	0	1112210000
					41	18	Negative.	+	
					56	17	Negative.		
71	32 years.	M.	W.	April, 1920.	7	3	Negative.	0	1111100000
72	3 years.	F.	W.	July 17, 1919.	1	2	Negative.	0	1100000000
					3	23	.....	+	
					5	59	.....	+	
					7	96	.....	+	
					12	72	.....	+	
73	9 years.	M.	W.	February 8, 1920.	7	1	Negative.	+	1111100000
74	42 years.	M.	W.	January 20, 1921.	19	27	Negative.		
75	13 years.	M.	W.	January, 1921.	11	280			
76	19 years.	M.	W.	December, 1920.	60±	18	Negative.	0	0000000000
77	10 years.	M.	W.	February, 1921.	7	114	Negative.	+	0000000000
78	6 years.	F.	W.	December 15, 1920.	42	5	Negative.	0	1111100000
79	8 years.	M.	W.	February 7, 1921.	4	70	Negative.	+	1111100000
80	5 weeks.	F.	B.	January 28, 1921.	5	270	Negative.	+	
81	8 years.	M.	W.	January 17, 1921.	14	8	Negative.	+	0000000000

diversity of the neurological symptoms encountered. Moreover, these changes are produced by a virus which is capable of damaging functionally important brain areas without necessarily producing permanent anatomical changes (Marinesco[8]). It has been demonstrated, furthermore, both by clinical and histological methods that as one affected area of the nervous system is recovering another area may be attacked, thus adding, in certain instances, new clinical features to an already complicated symptom complex. It is apparent from these considerations, therefore, that the chief characteristic of the malady is the kaleidoscopic appearance of transient neurological symptoms dependent chiefly on alterations in the midbrain and the basal ganglia, and in some instances in the spinal cord and peripheral nerves (Burrows[27]).

In this report no attempt will be made to construct clinical types of the disease depending on the prominence of this or that symptom complex. The important symptoms, however, will be discussed seriatim and illustrated when possible by case reports.

SYMPTOMS AND TYPES OF ONSET

It is not necessary here to discuss the various symptoms encountered during the early stages of the affection except in a general way, because the sequence of events at onset is clearly set forth in the detailed case histories recorded below.

However, it will be advantageous to call attention to a general division of symptoms at onset which is necessary for a proper understanding of the disease. These manifestations fall into two fairly well defined groups as follows: First, those dependent on a general reaction of the individual to an acute infectious disease; and second, those referable to involvement of the nervous system. These symptoms are fever, headache, malaise, nausea and vomiting, abdominal pain,

irritability and restlessness. In children delirium and convulsions were also frequent at the onset. Drowsiness, insomnia, diplopia and other visual difficulties, involuntary movements, muscular jerkings, tremors, spasticity, root pains, general weakness and psychoses occurred with especial frequency.

The onset may be abrupt or gradual, but in general a period of time elapses between the appearance of the general symptoms of infection and the development of the neurological symptoms.

Disturbances of General Consciousness

Disturbances of general consciousness often combined with psychical disorders have been prominent features of the clinical course in most instances. No constant type of disturbance has been encountered but, on the contrary, all gradations between sleeplessness at one extreme and coma at the other have been observed.

In a few cases sleeplessness of days' or weeks' duration was present and preceding or subsequent lethargic states were not observed. The following case may serve as an example:

Case 1.—W. J., a white boy, aged 4 years, was admitted to the Harriet Lane Home April 23, 1920, because of inability to sleep at night. He had been perfectly well until January 16. That evening he was not able to go to sleep and since that time this condition had persisted. Because of this nocturnal restlessness and activity, he was thought to have chorea. The mother stated that the child stayed awake all night spending the time in constant activity, talking, playing, singing, whistling, etc. Toward morning he would go to sleep and sleep a variable length of time, sometimes all day, sometimes only an hour or so during the entire 24 hours. Various means to combat the insomnia had no effect whatsoever, nor did keeping him awake during the day induce sleep at night.

Paralyses had never been noted. Examination on admission showed a well-nourished boy. No definite abnormal findings were obtained on physical examination. The cerebrospinal fluid was normal. The behavior of the child, however, was very striking. As night-time approached, he became very active, jumping up and down in bed and talking incessantly. He would often stay awake all night, at times talking to himself, at other times whistling and singing, fretting and crying, but never lying absolutely still. He spat a good deal both in the bed and on the floor. He would frequently wet the bed. When excited, he would stammer. The greater part of the night would be spent in ceaseless activity. Toward morning he would fall asleep. As a rule he slept from 3 to 12 hours in the 24; always between 5 a. m. and 6 p. m. The striking point about his sleep in the daytime was that it was very deep and when awakened for meals he would fall asleep immediately, sometimes in the act of eating. It was found very difficult to keep him awake during the morning. On awakening he would behave quite normally until evening when the same behavior would be repeated. Continuous tubs and packs were unsuccessful in bringing on sleep. He was discharged July 11, without any definite improvement in the insomnia. Since his return home there has been but little improvement in his condition.

Again, the insomnia of the acute stage of the disease might be followed by lethargy of several weeks' duration as in the following case:

Case 2.—W. D., a white boy, aged 11 years, was admitted to the Harriet Lane Home February 21, 1920. The past history was uneventful. On February 19, 1920, while at school, he became very excited and talkative and was sent home. His mother noted that he was irrational at times. The following night he became delirious. There had been no convulsions. Examination on admission showed a well-nourished boy, in active delirium, thrashing about in bed. There were no abnormal physical findings. The leucocyte count was 9800. The cerebrospinal fluid was normal (for subsequent examination see C. S. F. chart). The temperature was 100° F. but rose rapidly to 104° F., remaining there for six days, gradually falling to normal on the 15th day, with frequent slight elevations thereafter. He remained in active delirium for seven days, muttering constantly and pulling at the bed clothes. Typhoid fever was suspected, but excluded by the various laboratory examinations. Following the subsidence of the delirious state the patient passed into a state of lethargy in which he remained for ten weeks. At first he could be aroused and made to respond to questions, but he soon passed into deep coma, so that for five weeks it was necessary to administer both food and fluids by gavage. The mask-like facies during this period was striking (Fig. 1). Beyond the somnolence no striking neurological features were made out, until March 12, when external strabismus, a bilateral ankle clonus and a positive Babinski were noted. Hyperpnœa followed with diminished bicarbonate content of the blood serum (26 volumes per cent (Van Slyke)), which was not relieved by sodium bicarbonate. In spite of the administration of 1000-1500 calories per day by gavage, the patient lost considerable weight. From the first of May, he gradually improved, responded to questions, talked and moved his limbs. The ankle clonus, Babinski and strabismus disappeared. The facies remained, however, immobile (Fig. 2). He was allowed to leave his bed and was discharged June 20, apparently well save for weakness and general spasticity. By July he was walking about the house and sleeping well at night. When seen in August, there was noted a slight tremor of the hands and constant clearing of the throat. There were no abnormal movements. He had developed the habit of spitting and was disobedient at times. There was general spasticity and marked stiffness of the carriage in walking. The speech was monotonous (Fig. 3). In September he developed sleeplessness at night, which, though less marked, was still present when seen in December. At this time he seemed fairly well, but was disobedient. He was permitted to go to school.

Sleeplessness at night alternating with deep sleep during the daytime was a characteristic symptom in a few cases during the acute stage and also during the period of convalescence (*v. i.*, under Insomnia).

In other instances drowsiness or sleepiness of a few hours' or a few days' duration often combined with transient diplopia were the only symptoms of a very mild form of the disease.

Case 3.—M. E., aged 12 years, was admitted to the hospital October 30, 1919. He complained of dizziness. He had not had influenza. On October 22, 1919, he had double vision but went to school. He came home and slept all the afternoon. The drowsiness increased steadily until admission. On examination the patient was drowsy but clear when aroused. The legs and arms were somewhat spastic and there was a positive Babinski on the left. The spinal fluid contained 10 lymphocytes per c.mm. The patient slept constantly for four days. Thereafter recovery was rapid and complete.

Case 4.—M. C., a white girl, aged 16 years, was admitted to the hospital November 22, 1919. She had not had influenza. From November 8 to 17, 1919, she felt abnormally sleepy and slept several afternoons. On November 17 she noticed diplopia. This lasted several days, then disappeared, to return again November 21, 1919, for a few hours. The patient returned to school and has remained well (August 30, 1920).

Lethargy was present in many cases and in the severe forms of the disease was usually followed by deep coma.

CASE 5.—A. V. F., a white girl, aged 6½ years, was perfectly well until the evening of November 9, 1919, when she complained of slight headache and had fever. The following day she had a generalized convulsion and was unconscious for the remainder of the day. Following this she became stuporous with periods of consciousness, but at all times was difficult to arouse. There were no further convulsions and no vomiting. The patient was admitted to the Harriet Lane Home November 13 on the fifth day of her illness. Examination at this time showed a poorly nourished girl lying in a state of deep stupor. When stimulated she cried out but immediately relapsed into stupor. There were no evidences of paralyses either of cranial nerves or of the extremities. The left arm, however, was held stiffly and there was a tremor of the left hand. The reflexes were active; there was a positive Babinski on both sides and a slight ankle clonus on the left. Examination was otherwise negative except for otitis media on the left. The leucocyte count was 12,000 and the spinal fluid was normal. The Wassermann test was negative with blood and spinal fluid. The child then went into a deep lethargy so that she would not be aroused. She lay perfectly still, making no voluntary movements and was apparently unable to swallow solid food. There was a fine tremor of the tongue and of the hands. The ankle clonus and positive Babinski persisted. At times there was flexibilitas cerea. By December 9 the patient had become brighter and cognizant of her surroundings. The evidences of pyramidal tract involvement had disappeared. By the middle of December she had recovered and was able to sit up. At this time she developed a mild arthritis of the right shoulder and of the right hip. She was discharged January 13, apparently well. Since this time reports from her parents indicate complete recovery without sequelæ.

CASE 6.—A. R., a white male, aged 65 years, was admitted to the hospital October 22, 1919, complaining of dizziness and trouble with vision. The present illness began two months before admission with sleepiness and drowsiness which had constantly increased. On October 19, 1919, he felt dizzy and weak and stopped work. On examination his temperature was 103.7° F. and he was comatose. He muttered incoherently. There was bilateral ptosis. The pupils were active and the fundi normal. Coarse muscular jerkings of the arms and legs were observed. The extremities were fairly spastic. The tendon reflexes were normal. The spinal fluid contained 200 cells per c. mm. and a trace of globulin. The temperature remained above 102° F. The patient sweated profusely and emaciated rapidly. He died November 4, 1919.

Autopsy (Figs. 4 and 5).—The brain appeared normal in the gross. Microscopical sections showed marked perivascular infiltration about many of the small vessels in the caudate nucleus, lenticular nucleus, substantia nigra and mid-brain.

Characteristic, then, of the disturbances of general consciousness which may occur in the course of this disease are:

1. The variation of the disturbance from sleeplessness to coma with the intermediate stages which are called apathy, drowsiness, sopor, lethargy, stupor, etc.

2. The long duration of the lethargic state in many instances. A patient may lie for weeks or even months in a state of deep lethargy varying but slightly from day to day or week to week.

3. The fact that many of the patients, although apparently in a state of deep sleep, will respond promptly to a command or reply to a question in a perfectly rational manner, relapsing immediately into the former state of lethargy.

4. The frequent association of a state of general spasticity.

Lethargic states resembling those present in this affection may be observed in a number of acute diseases, such as typhoid fever, and in chronic affections, such as syphilitic basilar meningitis. However, they usually lack the characteristics outlined above, although sometimes the differentiation cannot be made until the patient has been observed over a considerable period of time.

Disorders of psychical activity, when present, are generally combined with some of the disturbances of general consciousness described above. The psychosis in a few instances was the only important symptom and a group of such cases has been reported from this hospital by Hohman.[28] In the majority of our patients, however, abnormal mental reactions, when present, were incidents in the unfolding of the symptom complex of the disease. We shall discuss here only a few of the more frequent mental symptoms encountered during the early stages of the malady. Delirium was infrequent in the adult cases, but was observed often in the early stages of the disease in children (see Case 2).

In the following case there were few symptoms other than delirium and excitement to suggest the diagnosis of epidemic encephalitis:

CASE 7.—W. H. E., a white male, aged 24 years, was admitted to the hospital January 27, 1920. The past history was unimportant. The present illness began January 25, 1920, with moderate fever and general malaise. A few days later he had aching of the limbs. Moderate delirium soon appeared, accompanied by visual and auditory hallucinations. The patient was restless and very talkative and confabulation was a striking feature. Transient diplopia, moderate tremor of the hands and slight nystagmus were present. The spinal fluid contained 30 cells per c. mm. The Wassermann test with the blood and spinal fluid was negative. When last seen, January 1, 1921, the patient was mentally clear but restless, talkative and rather expansive. He was also suffering from marked insomnia.

Other patients had irrational periods of variable duration with visual and auditory hallucinations. Occupational delirium was occasionally observed and in rare instances mental reactions not unlike a Korsakoff psychosis were present. One patient worked in the wheat field for days at a time. Another prayed constantly because voices told him "to get right with God." A young colored girl knew someone was hiding in the room waiting to kill her. Spontaneous, unprovoked outbursts of laughing or crying were present in several of our patients. These attacks were not provoked by adequate emotional stimuli and must be looked upon as abnormal. It is of interest that many of these patients had a mask-like facies and bilateral rigidity of slight extent (pseudo-bulbar syndrome).

It is not necessary at this time to detail all the mental symptoms encountered; a full discussion of this phase will be found in the papers by Abrahamson,[29] Hohman [28] and others.[30]

OCULAR DISTURBANCES

Disturbances of innervation of the extra-ocular muscles were often present during the active stage of the disease. *Diplopia* was frequently the first symptom referable to involvement of the nervous system noticed by the patient and in some instances preceded the appearance of any other symptoms by many days. The characteristic feature of these palsies was their transient and variable character. Thus, in

some cases diplopia was present on one examination and absent the next, or an internal strabismus, present for a short time, was followed by an external strabismus of variable duration. Furthermore, although most of the muscles innervated by the third nerve might be palsied successively, it was rare indeed to observe involvement of all of them at the same time.

Ptosis was frequent, usually bilateral, although often more marked on one side. It was seldom complete. It frequently contributed considerably in the production of the expressionless facies of the patients. In some instances it was impossible to decide whether the slight bilateral ptosis was dependent on faulty innervation or on lethargy, for drooping of the upper lids occurs in the somnolent state.[31]

Disturbances of associated eye movements were comparatively rare. One patient could not rotate the globes above the horizontal plane. A few had weakness on lateral deviation. Inability to converge was common, although usually transient.

We encountered a few instances of paralysis of accommodation. These patients complained of inability to see near objects clearly and to read fine print. In such cases we assumed that true paralysis of accommodation was present, unless there were optic nerve changes or conspicuous disorders of innervation of the extra-ocular muscles.

Nystagmus was present in a large number of cases and was of two types. In the first, it was similar to that observed in *early multiple sclerosis*, viz., the common rhythmical oscillations with a quick and slow phase. In the second, the eyes seemed as if held in place by springs, and attempts at fixation produced wide, irregular oscillatory movements of the globes in all planes, including the *anterio-posterior*, until the eyes came to rest, often in good alignment. The characteristic quick and slow phases were absent in such cases. Rarely, attacks of coarse jerking of the globes occurred without obvious provocation. So far as we know, this phenomenon has not been described in any other disease. Sicard and Kudelski [32] gave the name ocular myoclonia to this type of nystagmus.

Ophthalmoscopic examinations were made repeatedly in most cases. Hyperæmia of the discs was occasionally present. Optic neuritis with swelling of the discs was observed in the following case and also in Case 23 below:

Case 8.—E. F., male, white, aged 37 years, was admitted to the hospital July 29, 1920, complaining of headache. The present illness began February 1 with dizziness and weakness. About March 1 walking became difficult and he had pain in the back. For several days there was incontinence of urine. Frontal and temporal headache was constant; the left arm became weak and there was some dimness of vision. He noticed a few muscular jerkings. Examination showed a mask-like face with slight bilateral ptosis. The left optic disc was raised and hyperæmic; the edges were indistinct. The right disc was normal. There were no muscular jerkings. The spinal fluid contained 70 lymphocytes per c. mm. and a trace of globulin. There was no fever at any time. The patient was often irrational at night. He improved slightly and left the hospital against advice August 16, 1920.

Disorders of Motility

Disorders of motility were present in the majority of our cases. They were so diverse in character that it is impossible to classify them in well-defined groups. For descriptive purposes, however, we shall group all the motor phenomena under three heads as follows:

1. Disorders of tonicity.
2. Paralyses and Pareses.
3. Hyperkinetic phenomena.

1. *Disorders of Tonicity.*—At the onset of the malady general spasticity associated with other evidences of meningeal irritation, the so-called meningismus, may be present, as in the following case:

Case 9.—K. R., a white girl, aged 6 years, was admitted to the Harriet Lane Home September 19, 1920. She had been well until September 16 (three days before admission) when she complained of headache and vomiting. Throughout the day she was nauseated, drowsy and had no appetite. Toward evening her neck became stiff and a physician who was called regarded the condition as due to meningitis. The patient soon became unconscious but there were periods when she could be aroused. Examination on admission showed a poorly nourished white girl lying in a stuporous state with head retracted and back somewhat stiff. When spoken to she opened her eyes, relapsing immediately into stupor. There was retraction of the neck and apparently pain on flexion. There was no evidence of paralysis, the reflexes were active and there was a suggestive Kernig sign. The leucocyte count was 12,000; the spinal fluid showed 14 cells per c. mm. and a faintly positive globulin reaction. The temperature was normal. The Wassermann test was negative with the blood and spinal fluid. The evidences of meningeal irritation quickly passed away and by September 21 the patient had come out of her stuporous state and appeared bright. A second lumbar puncture done on September 23 showed 26 cells and a positive globulin reaction. The patient was discharged September 30 and has remained well since that time.

Later, however, evidences of disturbance of the pyramidal or extra-pyramidal motor tracts may appear. The former will be discussed with the paralytic phenomena and we shall therefore confine our attention here to those disorders of tonicity which may not be associated with evidences of pyramidal tract involvement.

(a) *Hypotonicity*, associated with ataxia or weakness of the extremities, was present in the following instance:

Case 10.—R. W., a white woman, aged 24 years, entered the hospital in March, 1919, complaining of jerking of the eyes and inability to stand. In October, 1918, she had had a febrile disease, called influenza, which had kept her in bed a week. February 23, 1919, she had severe headache and dimness of vision. Her eyeballs and eyelids were in constant motion. She felt poorly and went to bed, where she remained until admission to the hospital. About two weeks after the onset her legs seemed stiff and she could not walk. Her jaws jerked violently so that speaking was difficult. Since March 24, 1919, she had been unable to stand alone or to walk. Examination showed a well-nourished woman, mentally clear, not drowsy. There were frequent spasmodic contractions of the jaw and eyelids. The eyeballs jerked violently in all directions, both spontaneously and on attempts at fixation. Upward deviation was limited. There was slight bilateral ptosis. The speech was thick and scanning. The right abdominal reflex was not obtained. The muscles were markedly hypotonic and the movements were inco-ordinate. The spinal fluid contained 17 cells per c. mm. and a considerable amount of globulin.

The Wassermann test with the blood and spinal fluid was negative. There was a slight elevation of temperature during the first two weeks. At intervals the patient was drowsy; at other times there were attacks of unprovoked laughing and crying. By July 5, 1919, the jerking of the jaws had ceased and the jerking of the eyeballs was less marked. The incoördination had improved considerably and the patient could walk a few steps alone. It is possible that the hypotonicity, incoördination, scanning speech, nystagmus and motor weakness were dependent on a cerebellar localization of the process, but of this we have no definite proof. However, the resemblance to certain cerebellar syndromes is striking.

(b) *Hypertonicity*, often widespread, was a more frequent symptom. It was present in all the severe or fatal cases and often associated with waxy flexibility, as in the following instances:

CASE 11.—C. B., a white man, aged 36 years, was admitted to the hospital in March, 1920. The past history was unimportant. The present illness began March 12, 1920, with fever and dizziness. The family noticed that the patient was restless, euphoric and talkative. He complained of pain in the elbows and general tremor. On March 29 his speech was thick and there was inability to swallow. There was double vision. When first examined March 30, 1920, the patient was well oriented but depressed. There was marked tachypnœa and attacks of "smothering." The pupils were unequal. There was slight nystagmus. Dysarthria was present and the patient was unable to swallow. The face was mask-like. There was slight strabismus. The tendon reflexes were normal. There was very marked general rigidity with waxy flexibility. The patient remained in about the same condition for nine months. Incontinence of urine and feces was present at all times. The rigidity persisted and was of so high degree that he was practically incapable of voluntary motion. He was fed by gavage. The face was expressionless and speech was absent or markedly dysarthric. At times there were attacks of fever, often associated with tachycardia and marked tachypnœa and hyperpnœa of several days' duration. The respiratory rate was 50 per minute for several days. The patient at present (after a year) is a rigid vegetating organism incapable of voluntary motion or of continuous thought.

CASE 12.—C. D., a colored man, aged 35 years, complained of difficulty of vision of four weeks' duration. The present illness began March 27, 1920, with pain over the heart which lasted a day. The next day he felt giddy and sleepy but continued to work. That evening he had diplopia and was told his eyes were crossed. On examination the face was expressionless and mask-like. There was bilateral ptosis with weakness of both external recti. There was paralysis of accommodation. There was a coarse, irregular nystagmus and tremor of the lips and tongue. Coarse tremor of the arms was also present. The tendon reflexes were active. There was slight catatonia. The blood and urine were normal. The cerebrospinal fluid contained six cells per c. mm. and a trace of globulin. The Wassermann test was negative with the blood and spinal fluid. The lethargy increased and generalized spasticity appeared. The facial muscles became weak and transient dysphagia appeared. The patient was clear mentally until a few days before death. Rhythmical to and fro movement of a hand, arm or leg, and myoclonic movements of muscle groups were frequently observed. There was no fever. Lethargy increased to coma and the patient died two months after the onset of symptoms.

In other instances hypertonicity occurred in association with a coarse Parkinsonian tremor and a mask-like facies—the so-called Parkinsonian type of the disease. This syndrome occurred both in adults and children * and was often present for a considerable period of time. Indeed, Souques, Moreau and Pichon [23, 24] state that they have observed instances of epidemic encephalitis followed by true paralysis agitans. However, this observation needs confirmation, for these are the only cases that we could find in which the syndrome persisted. Even in these a sufficient period of time has not elapsed to form a definite conclusion.

2. *Paralyses and Pareses.*—Paralyses of upper or lower motor neuron type may be present during the active stage of the disease.

(a) Monoplegias, hemiplegias, paraplegias or diplegias associated with exaggerated tendon reflexes and other evidences of pyramidal tract involvement may occur. In most instances they were of short duration, followed by complete recovery. The following cases illustrate this type of motor disturbance:

CASE 13.—C. B., a white boy, aged 5½ years, had been well until February 6, 1920, when he complained of headache and had fever. The following day he seemed better but that afternoon he vomited and had a general convulsion. Following this he became drowsy and the convulsions became more numerous, occurring every few minutes. He was admitted to the Harriet Lane Home February 9. Examination at this time showed a fairly well-nourished boy lying in a state of coma. Convulsions similar to the type described occurred at five to ten minute intervals. Examination was otherwise negative. These convulsive attacks became less frequent and ceased February 11. The following day he regained consciousness and performed voluntary movements. There seemed to be weakness in the left hand, but otherwise no paralysis was noted. The spinal fluid on admission showed 55 cells per c. mm. and a positive globulin reaction. The temperature was about 101° F. for the first three days after admission and gradually fell to normal. The patient improved, became bright and co-operative. The weakness of the left arm, however, persisted. He was discharged March 14. When seen in September, the patient was quite well and the weakness in the left arm had entirely disappeared.

CASE 14.—M. J., a white boy, aged 8½ years, had been well until May 1, 1920, when he complained of slight headache and of burning of his eyes. The evening of May 18 he behaved queerly. He seemed dazed and would not respond to questions and the mother noted twitching of the right side of the mouth; he rapidly became unconscious and was brought to the Harriet Lane Home. Examination at that time showed a well-nourished boy lying in a stuporous state, from which he could be aroused at times in response to stimulation. Involuntary movements were noted which were almost entirely of the left side. The temperature was 100° F. but rose rapidly to 105° F., and then gradually fell, becoming normal on the sixth day after admission. The leucocyte count was 19,000. The spinal fluid showed 50 cells per c. mm. and a positive globulin reaction. The Wassermann test was negative with the blood and spinal fluid. There were no further convulsions but shortly after admission a right hemiplegia was noted. This, however, was transient and on the following day there were no evidences of weakness. On this day the child roused from his stupor, seemed bright and mentally clear. He was discharged perfectly well June 2. When seen three months later he showed no evidence of his former illness.

CASE 15.—R. A. G., a white girl, aged 1½ years, had developed normally and was perfectly well until September 17, 1920. At that time she became irritable and a few days later the mother noticed that the child was feverish. On September 24 she vomited and the fever continued, reaching 103° F. On September 26 the child could not walk because of stiffness of the right leg. The left leg became involved the following day. This spasticity relaxed during

* See Case 2 above.

sleep, but even then spasmodic contractions were noted which were severe enough to awaken the child. *Examination on admission* showed a well-nourished female infant, conscious and very irritable. The legs were extended and markedly spastic, and passive motion of the limbs evidently caused pain. There was a peculiar brawny condition of the skin and subcutaneous tissue. The deep reflexes were hyperactive, the Babinski and Kernig signs were negative. The upper extremities were unaffected and there was no evidence of cranial nerve involvement. The temperature was 101° F., the leucocyte count was 8500 and the spinal fluid showed 33 cells per c. mm. and a negative globulin reaction. There was no incontinence. This spasticity and general irritability became less marked by October 2 and the patient was able to walk with assistance. She was discharged and in two weeks was walking in a normal manner. At this time restlessness and wakefulness at night were noted. The child would sleep well until midnight but during the remainder of the night was wakeful. This wakefulness was not relieved by the administration of chloral hydrate. Gradually, however, this condition subsided and at the present time the child sleeps well and there are no evidences of residual paralysis.

(b) *Cranial nerve palsies* were present at some time in the majority of cases during the active stage of the disease. As a rule they were transient or recurrent and referable to involvement chiefly of the third, fourth, sixth and seventh cranial nerves or their tracts. Since these have been described above, we shall group together here the disorders of motility dependent on faulty innervation of the facial, masticatory and bulbar muscles.

The mask-like facies was so frequent that the diagnosis without that symptom was hazardous. The photographs (Figs. 1, 2, 3, 6, 7, 8, 10) show clearly this striking feature. The cause of the phenomenon is not clear. It was associated constantly with defective mimicry.

Dysarthria was present in a number of cases. As a rule, the patients complained that the tongue felt thick and the face stiff. In a few instances it was dependent on twitching of the muscles of the tongue. Dysphagia was often combined with the dysarthria as in Cases 11 and 26 and the following case, No. 16:

Case 16.—W. D., a white male, aged 24 years, was admitted to the hospital December 31, 1920, complaining of giddiness. In October, 1920, he had an acute febrile illness for three days. The present illness began rather suddenly December 17 with roaring in the left ear. On the following day he had intermittent attacks of pain down the left arm and behind the left ear. December 21 he had diplopia and "thickness of the tongue." He also noticed that he could not hear well. Drowsiness became marked and there were frequent painful jerkings of the left arm. He also developed difficulty in swallowing and a nasal voice. Difficulty in starting urination soon appeared. Examination showed a drowsy and dull patient with a mask-like face. He was clear when aroused but was partially deaf. The left pupil was larger than the right and there was slight nystagmus. Both optic discs were slightly hyperæmic. There were a few coarse non-rhythmical fascicular twitchings of the muscles of the face and limbs. The reflexes were normal except for a positive Babinski on the left. Mastication and swallowing were possible but were performed slowly and carefully. There was marked disturbance of pronunciation of the labials and linguals. He complained of numbness of the face and tongue. His temperature was 102° F., but in four days reached normal. The spinal fluid contained 26 lymphocytes per c. mm., and a slight increase of globulin; the gold chloride curve was normal. The Wassermann test was negative with the blood and spinal fluid.

Unilateral and bilateral facial weakness was frequent and often transient. The following case is a good example:

Case 17.—M. H., a white infant, aged 7 weeks, was admitted to the Harriet Lane Home April 4, 1919. She was born at term and had been considered normal until the first of April when she became dull and drowsy. Following this she could not be roused; there was slight fever. Examination on admission showed a well-nourished infant in coma. When stimulated she became spastic, but when relaxed had the appearance of a sleeping infant. Examination showed right facial weakness, bilateral ptosis, and slight general spasticity (Fig. 6). The temperature was 101° F. on admission but fell within 24 hours to normal. The leucocyte count was 8500 and the spinal fluid showed 28 cells per c. mm. and a faintly positive globulin reaction. The child improved and became less drowsy and the facial weakness and spasticity disappeared. She was discharged May 3, 1919, and did well at home. She died in June following an acute illness, the details of which were not obtainable.

Trismus, associated with tender masseters, was present in the following instance:

Case 18.—M. W., a colored woman, aged 28 years, was admitted to the hospital May 14, 1920. Four days previously her mouth and tongue had become very sore on attemps to move them and she was unable to open her mouth on account of pain. On examination the temperature was 99° F. but soon reached 102.5° F. The masseters were very tender on pressure and the patient could not open her mouth. She was drowsy and there was dysarthria. There was a double external strabismus which developed under observation. There was incontinence. The cerebrospinal fluid contained 5 cells per c. mm. and a trace of globulin. The reflexes were slightly hyperactive. The Wassermann test was negative. May 15, 1920, the fever reached 103.5° F. and the patient died suddenly.

Tachycardia was occasionally observed and in some instances was possibly referable to involvement of the vagus.

Hyperpnœa was present in six of our cases and deserves special mention. In each of these this symptom occurred during the early stages of the disease and was associated with a diminished bicarbonate content of the blood plasma. However, in several instances it was not relieved by the administration of sodium bicarbonate. The hyperpnœa was therefore not the result of acidosis but dependent on disturbance of the central respiratory regulatory mechanism. Brief records of patients manifesting this symptom may be of interest.

Case 19.—J. C., a colored man, aged 19 years, was admitted to the hospital March 4, 1920. The patient's mother stated that "he sees double and talks out of his head." The present illness began March 1, 1920, with staggering following a slight injury to the head. The next day the patient was irrational, weak and drowsy, and complained of double vision. On examination he was very lethargic and talked irrationally. When aroused he was rational and talked in a low monotonous tone. The face was mask-like (Fig. 7). There was bilateral ptosis with slight internal strabismus. There were many coarse jerkings of the muscles of arms, legs and abdominal wall. The reflexes were normal. The leucocyte count was 11,400. The cerebrospinal fluid contained 368 cells per c. mm. The globulin test was negative. The Wassermann test was negative with the blood and spinal fluid. The incoördination of the eye movements, slight nystagmus and fascicular twitchings persisted for many days. The temperature, which was 104° F. on admission, gradually returned to normal. The tachycardia and tachypnœa persisted; the respirations were usually about 36 to the minute. Lethargy diminished gradually. April 4, 1920, the patient was found in collapse. The respirations were very deep and more than 60 per minute. The pulse was rapid.

The CO_2 tension of alveolar air was 15 mm. Hg.; the bicarbonate content of the plasma was 40 volumes per cent (Van Slyke). Morphine gr. $\frac{1}{6}$ was given and this was repeated in one hour. The respirations fell to about the normal rate and the tachypnœa did not return. The patient gradually recovered and when last seen nine months after the onset of the disease was well except for a peculiar stiffness of carriage, an expressionless facies, and a few tic-like movements of the face.

CASE 20.—A. W., a white boy, aged 8 weeks, was admitted to the Harriet Lane Home April 16, 1920. He had been born at term and breast fed up to the onset of the present illness which had begun eight days before admission when it was noted he did not nurse well and had fever. Four days before admission he had a convulsion, which was followed during the next few days by a series of similar attacks, generalized in character. He refused to nurse. On admission to the hospital, examination showed a poorly nourished infant lying quietly in bed; there was marked hyperpnœa and general muscular rigidity. There was a transient ptosis of the right eyelid and hyperactive reflexes. Otherwise examination was negative. The temperature was normal. The leucocyte count was 22,000 and the spinal fluid showed 56 cells per c. mm. and a positive globulin reaction. The bicarbonate content of the blood was 28 volumes per cent (Van Slyke). There were no evidences of tetany. It was necessary to feed the child by gavage for the first 24 hours. In spite of the administration of sodium bicarbonate to the point of rendering the urine alkaline, the hyperpnœa continued. By April 20 this symptom had disappeared and the child was discharged in good condition except for slight spasticity. When seen November 30 he had completely recovered. (See also Cases 2 and 11.)

CASE 21.—A. Y., a white infant, aged 4 months, had been well until March 17 when following her bath she vomited and had a generalized convulsion. Following this she became unconscious and an internal strabismus was noted. She was admitted to the Harriet Lane Home the same day. Examination on admission showed a well-nourished female infant lying in an apathetic state; she could be aroused, however, and was rather fretful. There was definite hyperpnœa. A slight internal strabismus and ptosis of the left eyelid were noted; otherwise the examination was negative. The spinal fluid was normal. The bicarbonate content of the blood serum was 19 volumes per cent (Van Slyke). There was no acetone in the breath (Higgins). The urine was normal save for a few white cells and the phenolsulphonephthalein excretion was 65 per cent in two and a half hours. There were no evidences of tetany. On account of the hyperpnœa and the diminished bicarbonate content, sodium bicarbonate was administered by mouth to the point of rendering the urine alkaline, without effect on the hyperpnœa which continued when the bicarbonate content reached 48 volumes per cent (Van Slyke). Evidently then the acidosis was secondary to the hyperpnœa which was probably due to stimulation of the medullary center. The patient became less drowsy but the internal strabismus and ptosis persisted, and a slight facial weakness appeared. The hyperpnœa varied during the following three weeks; sometimes it was well marked, at other times slight. Several courses of sodium bicarbonate were given without effect. The spinal fluid on March 26 showed 20 mononuclear cells per c. mm., and a positive globulin reaction. On April 14 the child seemed brighter; the hyperpnœa, the ptosis and facial weakness had disappeared. The spinal fluid returned to normal and she was discharged with slight internal strabismus on April 28. She has since been entirely well.

(c) *Symmetrical paralysis* of peripheral nerve type was observed in six cases. These were characterized by a gradual onset, extensive flaccid paralysis of upper and lower extremities, more marked in the distal portions, slight sensory disturbances, muscular atrophy, and usually slow but eventual recovery.

CASE 22.—C. J., a white girl, aged 5 years, had been perfectly well until the onset of her present illness February 1, 1920, when she awakened complaining of aching in her knees. The following day the child appeared perfectly well but that night again complained of aching in her knees. On the third day her parents noted that the child walked stiffly. This stiffness increased and weakness of the legs developed to such a degree that three weeks after the onset the patient was unable to walk. No swelling or tenderness of the knees developed. The patient then complained of headache and about one week before admission weakness in the hands was noted. Beyond slight irritability, there was no change in the patient's mental condition. She was admitted to the hospital on March 25, seven weeks after the onset of her illness. Examination at that time showed a well-nourished white girl who was unable to stand, was quite irritable, but well oriented and apparently normal mentally. There was neither facial nor ocular paralysis but a general muscular weakness of upper and lower extremities. The legs were moved but little even on stimulation. There was some atrophy but this was not marked. The grasp of both hands was weak. There was ataxia. No disturbance of sensation could be demonstrated. The deep reflexes were absent at elbows, knees and ankles. The spinal fluid was under normal pressure with 6 cells per c. mm. and gave a strongly positive globulin reaction. The Wassermann test was negative with the blood and spinal fluid. The patient remained in the hospital one month. During that time the muscular weakness became noticeably less marked. This muscular weakness was symmetrical and more marked distally than proximally. The deep reflexes remained absent and there was never any sensory change. At the time of discharge, April 24, the patient could move her arms and legs well and could stand with assistance. By the middle of July she had recovered strength in her limbs and was able to walk with support. By September she was able to run and play with apparent control of her extremities, and by the last of November seemed completely recovered.

The other causes of symmetrical paralysis of lower motor neuron type were excluded in this case and there remained a widespread paralysis of upper and lower extremities developing rather suddenly with complete recovery.

CASE 23.—F. S., a white girl, aged 10 years, was brought to the Harriet Lane Home July 30, 1920, because of weakness. She had been well up to May 1, 1920. At that time she fell. A week after this she complained of headache and vomited. This was repeated several times. There was no fever. Her appetite became poor and on June 1 weakness in her legs was noted, at first only after walking. Subsequently this increased until she was unable to walk, and about the middle of July weakness was noted in the arms as well. There was no visual disturbance. Examination on admission showed a poorly nourished child with general muscular weakness. She was unable to walk without assistance and after making a few steps complained of feeling very tired. There were no cranial nerve palsies. The eyes reacted to light and on accommodation. There was a definite optic neuritis more marked on the right. The legs showed generalized muscular weakness with some muscular atrophy. The arms showed muscular weakness to a less extent with a very weak grip. The deep reflexes were all absent. The superficial reflexes were present. The spinal fluid was under slightly increased pressure with 28 mononuclear cells per c. mm. and a strongly positive globulin reaction. The Wassermann test was negative with the blood and spinal fluid. There was no disturbance of sensation, nor had the patient complained of any sensory disturbance. The child remained in the hospital until August 19. During this time her condition improved. The appetite became better. The optic neuritis became slightly less marked and the spinal fluid returned gradually to normal (see c. s. f. chart). The weakness of the arms and legs became definitely less, so that the patient was able to sit up without assistance and to walk a few steps. The knee kicks were still absent but the arm reflexes returned. There was a slight foot drop and some muscular atrophy particularly in the

hand. The galvanic stimulation of muscles of the legs gave the reaction of degeneration. This was not present in the muscles of the forearm. The patient was seen again September 22 and had improved during her month at home. She had been sitting up in bed but had not been allowed to walk. There was definite improvement in muscular strength and control, and she was able to sew. Ophthalmological examination showed a mild optic neuritis. There was an ataxic tremor of the hands with atrophy but no wrist drop; ataxia of the legs with definite improvement in muscular power. The deep reflexes were still absent. A letter from the mother on December 22, 1920, stated that the child was steadily improving, walking around the house without tiring and sleeping well at night.

In summary, an acute polyneuritis in a previously well girl with evidences of increased intracranial pressure, inflammatory reaction in the spinal fluid, optic neuritis, generalized muscular weakness of lower motor neuron type, more marked in the legs; absence of sensory disturbance, with recovery within seven months.

Case 75.—A white boy, aged 13 years, was admitted to The Johns Hopkins Hospital February 15, 1921, complaining of soreness in his back and legs. His past history was negative. The present illness began January 1, 1921, with pain while chewing. The next day he had tingling of his fingers, and a few days later numbness, pain and weakness of the legs developed. About that time he also had severe headache and pain in his back. Examination showed a well-developed boy. The fundi and ocular movements were normal. There was slight general atrophy of the muscles of the hands, feet, arms and legs. The muscles were tender on pressure. There was weakness of the muscles of the extremities and back and slight weakness of the muscles of mastication. Sensation was intact on objective testing. There was hyperæsthesia over the feet. There was no fever. The blood counts were normal. The Wassermann test with the blood was negative. The spinal fluid on the 11th day of the disease contained 280 cells per c.mm. and gave a positive reaction for globulin. The muscles of the legs and arms gave either complete or partial reaction of degeneration. The urine contained a few leukocytes. The boy left the hospital February 23, 1921 much improved. The tenderness on pressure had disappeared and he could rise to a sitting posture which was impossible on admission. By the middle of March the muscle strength had returned to such a degree that he could walk alone.

Case 25.—D. F., a white man, aged 37 years, was admitted to the hospital April 2, 1920. He complained of vomiting and numbness of the feet. The present illness began the middle of March, 1920, with "aching all over" especially of the legs and head. He felt feverish and had a chilly sensation. These symptoms lasted about a week, when repeated nausea and vomiting appeared. He became so weak that walking was impossible. On examination the patient was drowsy and answered slowly but accurately. The face was expressionless. There was slight nystagmus on upward deviation. The pupils were active and the fundi were normal. There were weakness and atrophy of the muscles of the feet, legs, hands and arms. Sensation for touch, pain and temperature and recognition of position was diminished below the knees and elbows. The knee jerks were sluggish; the ankle jerks were not obtained. The tendon reflexes of the elbows were present. The leucocyte count was 2840. The cerebrospinal fluid contained 70 cells per c.mm., with a trace of globulin. The Wassermann test was negative with the blood and cerebrospinal fluid. While the patient was in the hospital there was no fever. The calf and arm muscles wasted rapidly and the reaction of degeneration was present. The patient left the hospital against advice and died six days later.

Case 26.—A white man, aged 25 years, was admitted to The Johns Hopkins Hospital August 20, 1920, complaining of inability to walk. His present illness began in March, 1920, when he noticed that his hands were numb. He began to have pains in his arms, legs and eyes. Seven weeks before admission he had fever and chilly sensations. Three weeks later he had difficulty in speaking and trembling of the limbs and face. He soon developed hiccup, great weakness and difficulty in swallowing. He vomited frequently. On examination he showed poor memory and disorientation for time. The facial muscles were weak and deglutition and articulation were very difficult. The eyes were normal. The tendon reflexes were exaggerated and there was an equivocal Babinski sign. The muscles of the extremities were weak and there were numerous and widespread fibrillary twitchings. Reaction of degeneration was present in some muscles of the calves and arms. The leucocyte count was 6200. The cerebrospinal fluid contained 3 cells per c.mm. and gave a negative globulin reaction. Except for the rather abrupt onset the resemblance to progressive muscular atrophy was striking. However, when the patient was last seen, the fibrillary twitchings and bulbar palsy had disappeared and the muscles had attained nearly normal size and strength.

3. *Hyperkinetic Phenomena.*—Under this heading we shall describe a group of symptoms referable to neuromuscular hyperactivity which we have observed in patients with epidemic encephalitis. Recent medical literature contains many reports of cases presenting various types of hyperkinesias.[26] In some of these such names as "encephalitis myoclonica" and "encephalitis choreiformis" were employed to designate the disease type. In others the close resemblance of the involuntary movements to those observed in Sydenham's chorea,[25, 28, 39, 40] in Parkinson's disease,[38, 41] in Friedreich's myoclonia [27] and in other less well-known maladies,[26] has been pointed out. However, until the pathology of these phenomena is better known, it is not desirable to attempt to divide encephalitis into types depending on the character of the hyperkinesias. Furthermore, our knowledge of the pathological alterations in the large group of affections characterized by the presence of hyperkinetic phenomena is still too meager to allow completely satisfactory correlation of the clinical symptoms and structural alterations.

The hyperkinetic phenomena encountered during the active stages of encephalitis consist of non-rhythmical muscular twitchings, fibrillary twitchings, tremors, choreiform and athetotic movements, myoclonias and certain rhythmical spasmodic movements. In some instances, furthermore, convulsions may occur.

(a) *Muscular twitchings* were present in the majority of the adult cases, rarely in children. They may be fibrillary, fascicular or involve a whole muscle or group of muscles. In many instances only the muscles about the mouth or in the eyelids were affected, but in other cases the twitchings were widespread. The movements were quick, usually non-rhythmical and often violent. At times they were accompanied by pain. They differed from the more rhythmical myoclonias and also from the usual fine fibrillary tremors.

(b) In one case observed by us (Case 26) *true fibrillary tremors* of the muscles of the limbs and of the intrinsic muscles of the hands with widespread muscular atrophy were present. This patient also presented many other symptoms commonly observed in progressive muscular atrophy such as dysphagia, dysphonia and signs referable to pyramidal tract involvement, but it is fairly certain that the picture was pro-

duced by the virus of epidemic encephalitis. In the following case, also, fibrillary twitchings were observed:

CASE 27.—W. B., a white man, aged 26 years, was admitted to the hospital complaining of burning of the eyes. The present illness began three months before admission with "aching all over," shooting pains in the joints, burning of the eyes, and painful micturition. There were also photophobia and difficulty of vision. On examination the patient was drowsy and the face was expressionless. There was slight nystagmus. An occasional quick jerk of the right arm was observed. The legs were stiff and painful on passive motion. The arms were ataxic. The tendon reflexes were normal. There was numerous fibrillary twitchings of all the muscles of the extremities, especially of the interossei. The face was paræsthetic. The temperature occasionally reached 99.5° F. The spinal fluid contained 15 cells per c. mm. and a trace of globulin. The Wassermann tests were negative.

(c) *Tremor* was frequent, especially in patients with slight general spasticity. As a rule, it was rather coarse and fairly regular, but unlike that observed in paralysis agitans. In other instances fine tremor of the fingers was present. Types of tremor accentuated by voluntary movement (intention tremor), however, were not observed by us.

(d) *Myoclonia,* viz., rapid, rhythmical contractions of a muscle or group of muscles, with or without movement at the joints, was observed in a large number of cases. In some instances a rapid to and fro movement of a whole segment was produced by the involvement of synergistic groups of muscles. As a rule, the attacks of myoclonia were spontaneous, but in some instances they were precipitated by voluntary motion. Case 11, recorded above, affords a good example of this type of motor disorder, as does the following:

CASE 28.—E. T., a white girl, aged 3 years, was admitted to the Harriet Lane Home September 9, 1920. Previously the child had been well except for tantrums of crying and wanting her own way, which she had had for about a year. One month before admission she vomited and during the month this was repeated several times. On September 6 the child seemed sleepy and on the following day had fever and was unable to sit up. She remained drowsy but could be aroused. On September 8 twitchings about the mouth and slight tremor of the left hand were observed, which became more marked up to the time of her admission. Speech had become less distinct. There had been none of the temper tantrums since the onset of the present illness. Examination on admission showed a well-nourished girl lying in a state of semi-stupor, occasionally rising to a sitting position. There was constant twitching of the left side of the face and occasionally the muscles of the left side of the neck and deltoid and upper arm would twitch also. When offered an object, the child would grasp it with the right hand. There was general spasticity, more marked on the left. The deep reflexes were present, there was no clonus. The leucocyte count was 7000 per c. mm. and the temperature never went above 100° F. The spinal fluid was normal. The child remained in the hospital until September 30. During the first part of her stay the twitchings of the left face, arm and to a less extent of the leg were marked. A few days later, however, it was noted that the twitching was present also on the right side. There was no actual paralysis of any part. These muscular twitchings never involved all the muscles of an extremity at one time, but there would be twitchings of parts of one muscle group now here, now there. These movements resembled the muscular twitchings produced by a weak galvanic current. By September 30 they had entirely stopped and the patient was discharged apparently recovered except that she refused to grasp objects with her left hand. This condition was still present when she was last seen (January 6, 1921). There were no other sequelæ.

(e) *Choreiform movements* indistinguishable from those of acute chorea were present in a few cases. The following record demonstrates clearly the difficulties of diagnosis in such instances:

CASE 29.—K. B., a colored woman, aged 17 years, was admitted to the hospital March 23, 1920, complaining of jerky movements and pain in the neck. The patient was delivered by normal labor February 14, 1920. Nine days later she had sharp shooting pains in the limbs and neck. The pains recurred about every ten minutes and were very severe. She felt very weak. On March 18, 1920, the patient was delirious and her temperature had reached 105° F. Marked jerking of the arms, legs and body appeared. There was diplopia. Examination revealed violent, generalized, purposeless movements, indistinguishable from those in acute chorea. There was delirium with visual and auditory hallucinations. The patient was sure someone was in the room waiting to kill her. There was slight ptosis on the right. The spinal fluid contained 225 cells per c. mm. and a trace of globulin. Her temperature was 103° F. but slowly fell to normal. The violent choreiform movements gradually disappeared and the patient became lethargic. Succeeding the chorea extensive myoclonia was observed. The attacks of the latter occurred spontaneously or were precipitated by voluntary movement. They occurred in various groups of muscles. Following these, quick fascicular jerks were observed. The ptosis was variable—often bilateral. The face was expressionless and rigid and masseter tenderness was present (Fig. 8). From time to time sharp pains were present in the extremities. Marked internal strabismus appeared associated with coarse jerky movements of the globes in all directions, even anteroposteriorly. These were usually caused by attempts at fixation but were occasionally spontaneous. There was also coarse intention tremor of the arms. The symptoms gradually disappeared and when last examined eight months after onset the patient had practically recovered. The eyes still oscillated slightly and there was some strabismus.

(f) In the following instance peculiar movements consisting of *bilateral rhythmical tonic spasms* were observed:

CASE 30.—M. G., a colored woman, aged 27 years, entered the hospital October 5, 1920, unable to talk on account of peculiar motor phenomena described below. Her illness began October 1 with vomiting. In a few hours she was irrational and delirious. On examination the face was smooth and expressionless. There was slight nystagmus. The optic discs were very red, but the margins were sharp. About ten times every minute the patient had a tonic spasm consisting of bilateral contraction of the neck, abdominal and limb muscles. The contraction produced flexion at the neck, elbows, wrists, hips, knees and ankles. These spasms gradually became less severe and ceased. There was marked sweating, at first limited to the face but eventually involving the whole body. The patient was lethargic at intervals. Recovery was uneventful and complete.

The striking characteristic of these tonic spasms, whether limited to an extremity or generalized, is their rhythmicity. In the case just recorded they occurred every 5-6 seconds during one period of observation. Later they became less frequent but still remarkably rhythmical. In another instance only the left leg was involved and the spasm occurred every 3-4 seconds. Marie and Levy have given the name "bradycinesia" to this type of motor disorder.

(g) *Hiccup* of long duration, usually occurring in attacks alternating with free intervals, was present in the following instance:

Case 31.—A white man, aged 42 years, was admitted to the hospital October 6, 1919, complaining of hiccup and depression. The present illness began in September, 1919, with an attack of hiccup of three days' duration. Then there was a period of freedom for a week when the symptoms reappeared. The patient also felt weak and unsteady on his legs. He had a fine tremor of the hands and constant hiccup when first examined.

It is of interest that during the Canadian epidemic [44] of encephalitis a number of instances of continuous hiccup were observed. Their relationship to encephalitis is still obscure, for apparently no other symptoms referable to the nervous system involvement were observed. At the present time a widespread epidemic in which hiccup is the only symptom is present in the eastern part of the United States and in Austria.[45] Siccard [46] and others [45, 47] have called attention to the prevalence of epidemic hiccup in France and its relation to abdominal and diaphragmatic myoclonia.

(h) *Convulsions* were frequent at the onset in the young but occurred in only one instance in an adult. Case 13 illustrates a frequent form of onset of the disease in children.

A few generalizations may be drawn from the study of the hyperkinetic phenomena. First, a variety of movements may be present in one case. Thus choreiform movements may be replaced by myoclonia and this in turn by muscular twitchings. Secondly, none of these, with the possible exception of ocular myoclonia described above, is of much diagnostic importance when considered alone. However, a history of the sequence of events will usually direct attention to the probable diagnosis. Thirdly, a variety of disorders of motility have been observed as late symptoms or sequelæ of the malady. These will be discussed below.

Disturbances of Sensation

The sensory disorders encountered during the active stages of epidemic encephalitis are of considerable interest, although not frequent. In the early stage of the disease general hyperæsthesia, dependent in all probability upon meningeal irritation, is not uncommon. It is usually very transient. Occasionally also marked tenderness of the masseters may be demonstrated.* In one patient this phenomenon was so marked that chewing was impossible and the mouth could not be opened. The patient was given anti-tetanic serum, although a few hours later diplopia and strabismus developed.

Headache is a frequent symptom and although usually present only for a few days at the onset, may persist for weeks or months. In the later instances it may be considered as a direct neurological symptom and not as a part of the general reaction to the toxins.

Special interest is attached to a type of radiating pain, occasionally constant but more often paroxysmal in character, which resembles closely the familiar root pains of tumors of the cord or the lancinating pains of tabes dorsalis. This type of pain was usually present in those patients who later developed marked muscular twitchings or choreiform or myoclonic movements. The following case record is typical:

Case 32.—W. H., a white man, aged 23 years, was admitted to the hospital March 1, 1920, complaining of nervousness and drooping of the eyelids. He had had a mild attack of influenza in September, 1918. The present illness began February 22, 1920, with severe intermittent pain in the left ring finger which radiated upwards to the elbow. The pain occurred every 10-15 seconds and lasted in all two days. Following this he felt shaky and had a severe generalized tremor. Chewing was difficult. The speech was jerky. Drowsiness and diplopia appeared and the patient noticed that his eyelids drooped. On examination the temperature was 102° F. The face was expressionless and there was bilateral ptosis. The pupils were active. There was a coarse rapid tremor of the hands. The extremities were quite spastic. The tendon reflexes were very active and there were bilateral patellar and ankle clonus. The cerebrospinal fluid showed 25 cells per c.mm. and the globulin reaction was negative. The Wassermann test was negative with the blood and cerebrospinal fluid. The fever soon disappeared. The pains in the arms became less severe. The left forearm muscles became weak and the arm reflexes were increased on that side. The pain down the left arm was the last symptom to disappear. When last seen, eight months later, the patient felt much better, but had developed insomnia at night with drowsiness during the daytime. He was able to continue his medical studies.

In another patient the radicular pains in the limbs were followed by marked atrophy of the distal muscles of all the extremities associated with extensive fibrillary twitchings.

Numbness or paræsthesia of one-half of the body, of an arm, a leg or of the face, was occasionally complained of by the patient. Objective sensory disturbances, however, were seldom demonstrated in such instances.

The polyneuritic form of the affection, discussed above, may occur with sensory changes similar in all respects to those encountered in an alcoholic polyneuritis. In other cases of this form of the affection no sensory changes could be demonstrated.

Miscellaneous Symptoms

Sweating is often a prominent feature of the disease. In one instance (Case 29) it was limited to the face for several days but later became general. The gowns of some patients were constantly drenched with sweat, although they had little or no fever at the time (see Case 6).

Urinary incontinence was present in a few instances. As a rule the patients were comatose or very lethargic, but in other cases transient loss of sphincter control was probably dependent on involvement of the mechanism controlling the bladder and rectum.

Late Symptoms and Sequelæ

It might be expected that a disease characterized histopathologically by inflammatory alterations widely distributed throughout the nervous system would produce, after the cessation of the acute process, changes in the delicate regulatory mechanisms which manifest themselves in various psychic and neuromuscular disorders. Such, indeed, is the case. But the

* First called to our attention by Dr. H. M. Thomas.

chronicity of the disease, the development of new symptoms after apparent recovery and the rapid changes that may occur, lead us to believe that in many instances these apparent sequelæ are in reality evidences of a disease process still active.

The phenomena, described below, may appear at any time during the course of the disease. As a rule, however, they occur after the subsidence of the acute stage or after apparently complete recovery.

(1) *Psychic disorders* are present during the period of convalescence in a large number of cases. They consist of mental depression, a feeling of unreality and inferiority, changes in disposition, irritability, increased psychomotor activity, disobedience in children, inability to concentrate and often marked mental fatigue. Occasionally delusional and confusional psychoses may appear. Emotional instability consisting in uncontrollable laughing or crying is not uncommon. In some instances these mental residuals are not striking when the patient is in the ward. They appear, however, as soon as he returns to his home or his business. These unfortunates, usually aware of their abnormalities, often develop marked neurasthenic and psychasthenic states. The papers of Bramwell,[48] Claude,[49] Bergé and Hufnagel,[50] Papen *et al.*,[51] McNalty,[8] Abrahamson,[29] Leahy and Sands[52] and others may be consulted for interesting details of this phase of encephalitis.

(2) *Insomnia* as a late symptom or sequel of the affection is so characteristic, especially in children, that it will be discussed in some detail. During the active stage of the disease sleeplessness is often present, especially in instances of the disease in which hyperkinetic features were noted (McNalty,[8] Ellis,[53] McAlpine,[54] Sicard,[55] Boyd,[56] Laporte and Rouzaud,[57] Roger,[57] Dimitz,[15] Neal,[58] Abrahamson,[29] Findlay and Shiskin[59] and others). During the later stages, often some time after apparent recovery, a syndrome described by one of us in a previous report[60] may make its appearance.* This consists of sleeplessness at night alternating with marked drowsiness or even lethargy during the daytime which manifested itself as follows:

Towards night the parents note a change in the child's behavior; he becomes restless, excited and runs about the house prying into things. He will not obey. When put to bed he does not go to sleep but jumps up and down, shakes the bed, calls frequently to his parents, talks incessantly, sings, blows, whistles and spits on the floor. He becomes destructive, tears the linen, shouts, runs out of his room and when confined will not remain quiet. He spends the whole night in constant activity. He is able to recognize his parents but makes queer sounds and strange gestures. He frequently soils the bed, plays with his feces or masturbates. At dawn he falls asleep and is difficult to arouse. This sleep usually lasts until noon. When awakened during this sleeping period, he is stupid and falls asleep again during a conversation or examination. For a few hours in the afternoon he seems fairly normal, but at dusk the restless, sleepless period begins again. We have observed this symptom-complex in 12 children (and in a mild form in two adults), a remarkably high percentage of the total cases. The striking features of the syndrome are the similarity of behavior of the affected children and the chronicity of the symptoms. In none of them has a return to normal taken place (February, 1921), although improvement has been noted in some.

The symptom-complex may follow closely "recovery" from a typical acute attack, or develop late in convalescence; or it may even appear as the only recognizable clinical feature of the disease. It may not be as severe as outlined above, but be manifested as a mild disturbance in sleep of brief duration. Illustrative cases are as follows (see also Cases 1, 2, 7, 15 and 32 above):

CASE 33.—M. F. G., a white girl, aged 3½ years, had been well until late in February, 1920. At that time she complained of feeling tired and her parents would notice that frequently during the day she would lie down and sleep for a while and then get up and play again. She would do this from three to five times during the day. About the 1st of May she became restless at night and would not go to sleep before early in the morning. Bromides were ineffective. Towards the middle of May her mother noticed weakness of her legs and jerky movements of the arm when grasping objects. No strabismus or facial weakness had been noticed. She was admitted to the Harriet Lane Home for observation June 12, 1920. Examination at that time showed a small poorly nourished child, thrashing about restlessly in bed and quite irritable. However, she seemed bright mentally. Physical examination was negative except that the patient was disinclined to stand, although she would use her legs fairly well in bed. The deep reflexes were obtained with difficulty. The child did not sleep until after midnight. The spinal fluid was normal. A letter from the father December 22 says that the patient has greatly improved except that she does not always sleep well at night. However, she sleeps better than she did previously. She will occasionally drop off to sleep during the daytime. She was active and mentally normal.

CASE 34.—H. G., a white boy, aged 9½ years, had been previously well until February 27, 1920, on which night he was unable to go to sleep, was restless and had a peculiar staring expression. Since that time he had not slept well at night. A facial paralysis was noted by the mother four days after the onset. Up to the time of admission he had been going to sleep about 4 a. m., sleeping often until noon. He was admitted for observation July 13, 1920. Examination at that time showed a rather thin boy, somewhat apprehensive, with a definite left facial paresis (Fig. 9). The pupils were unequal, but reacted to light. There was definite internal strabismus and hyperactive reflexes. The spinal fluid was contaminated with blood. During the night in the hospital the patient slept very little. He was seen again in September, somewhat improved but he still remained awake most of the night, during which time he was excitable, in constant motion, wanting to do something all the time, but generally rational when spoken to. The left facial weakness was still present but very slight. He was said to be not as bright as he had been before his illness. No abnormal muscular movements had been observed, but at times there was increased salivation. His voice was monotonous and his expression blank and worried. A communication from his mother, December 27, stated that there was very little improvement. At times he seemed better, at others he relapsed into insomnia.

CASE 35.—C. J., a colored boy, aged 1¾ years, had developed normally and had been well up to March 1, 1920, when he had fever and was fretful. The fever subsided in a few days but toward the last of the month the child became very lethargic, sleeping most

* This syndrome has since been observed in various European countries. (See J. Am. M. Ass. 1921, LXXVI, 934.)

of the time. He refused food and seemed to have some difficulty in swallowing. There were no convulsions and he vomited only once, which was at the beginning of the illness. Examination on admission March 27, 1920, showed a well-nourished colored boy lying in a state of lethargy from which it was difficult to arouse him. The facial expression was quite blank with a flattening of the nasolabial fold suggesting a "mask-like facies" (Fig. 10). However, there was no paralysis present. The extremities were freely moved and the reflexes were active. The temperature was 100° F. The leucocyte count was 6000. The spinal fluid on admission showed 19 cells per c. mm. and a positive globulin reaction. During the day the patient would at times sit up in bed and occasionally stand. There was a ptosis of the eyelids and a lack of attention to his surroundings. His facial expression is well illustrated in the accompanying photographs. The patient had frequent attacks of naso-pharyngitis with elevations of temperature but gradually became brighter, took more notice of things and was discharged in good condition May 20. The following month he was admitted for tonsillectomy and appeared normal (Fig. 11). He did well until September 20 when he was wakeful and restless all night, tossing about in bed. Following this he did not sleep well at night, waking up generally around 11 o'clock, screaming and pointing at imaginary objects. Sometimes he would stay awake all night and at other times he would go back to sleep after a couple of hours of wakefulness. Occasionally during the waking period waving movements of the arms were noted. This condition gradually improved and when last seen, January 6, 1921, he was sleeping better, although he woke up every night for an hour or two. However, he was less irritable and excited than before. He had developed enuresis and the mother had recently noted an increased amount of saliva with drooling particularly at night.

Case 36.—H. W., a white girl, aged 9 years, had been previously well except for the ordinary exanthemata until March, 1920, when she had an acute attack of scarlet fever. She recovered from this and in April a tonsillectomy was performed. It was observed at this time that the child was restless at night and during the month of April jerky inco-ordinate movements were noted and certain tic-like movements such as constant pulling at her neck. From this time wakefulness had persisted. She generally slept four to six hours in the twenty-four, usually between 4 a. m. and 10 a. m. She gradually became more excited at night so that she was admitted to a private sanitarium on June 13, 1920. There was no history of paralysis or ocular symptoms. Physical examination at that time was entirely negative. During the day the child was bright and cheerful. As night came on, she became excited, over-active, laughing loudly at times, at others talking incoherently, standing up in bed, pulling at her neck, whistling and singing. She usually went to sleep about 3 a. m. The patient was placed in an ideal environment in a quiet place in the country with a special day and night nurse. However, there has been no material change in her condition and up to the present time she still suffers from inability to sleep at night.

Case 37.—B. J., a white boy, aged 6 years, had been perfectly well until February 3, 1920, on which day it was noted that he was restless and delirious. This excitable state lasted for three days and nights. During this time purposeless movements of the hands and arms were observed which had disappeared by February 20. At this time also a tremor of the hands was noted and a change in speech, the child talking much more slowly than formerly. No paralyses were noted, but inability to sleep, at night, developed. He was admitted to the Harriet Lane Home May 3, 1920. Examination at this time showed a well-nourished boy, apparently of normal mentality; his speech was slow and scanning and there was a coarse tremor of the hands. The cerebrospinal fluid showed 2 cells per c. mm. and a positive globulin reaction. The Wassermann test was negative with the blood and spinal fluid. The child remained in the hospital until May 31. During this time he slept fairly well at night, but the tremor of the hands and the slow scanning speech persisted. When seen July 15 this speech defect had entirely disappeared and the patient talked in a normal manner. He was bright and responded readily to questions. The tremor had also disappeared, but the insomnia had become worse, the patient usually getting to sleep at 2 or 3 a. m. and sleeping until noon the following day. This condition improved so that by September he was sleeping fairly well at night. A report from the parents stated that the child died the middle of November following an acute abdominal condition, the nature of which was not clearly understood. No autopsy was performed.

2. *Neuromuscular phenomena* of various types may appear during the period of convalescence and are rather characteristic of the disease. In general these consist of muscular twitchings or jerkings, tremors, choreiform and athetoid movements, ties, general psychomotor overactivity, spasticity and rarely paralyses (Buzzard and Greenfield,[61] Marie and Levy,[62] Sicard,[63] Netter,[64] Claude,[49] Papin *et al.*,[51] Lortat-Jacob and Hallez,[65] Kahn,[66] McNalty,[5] Leahy and Sands[52] and others).

A state of general psychomotor overactivity, characterized by restlessness, is often present. The patients seem unable to remain still; they must be doing something constantly and are always hurrying. Simple acts are performed with exaggerated movements. In one patient, an adult, this condition has been present for nearly eight months but is gradually disappearing. In children, due to lack of conscious control, this abnormal state is even more marked.

Tic-like movements are commonly present and have been described by various authors.[67, 68, 13] They consist in the frequent repetition of some act and are indistinguishable from the common tics of psychasthenics. The following cases illustrate these movements:

Case 38.—C. S., a white boy, aged 7 years, was admitted to the Harriet Lane Home February 24, 1920. He had been perfectly well up to February 19, at which time it was noted that he talked strangely. That night delirium, restlessness and muscular twitchings were noted. The following day the restlessness continued and a physician who was called thought the boy had chorea. After a sedative was given, the movements stopped, and the boy became stuporous. On admission to the hospital he was in stupor and slept a great deal of the time. However, he could be aroused and would respond to questions. There was no paralysis and the physical examination was practically negative. The temperature on admission was 103° F. It dropped in the course of five days to normal. The leucocyte count was 16,000 and the spinal fluid contained 36 cells per c. mm. and gave a positive globulin reaction. There were no choreiform movements observed in the hospital. The patient gradually recovered from his stupor and was discharged April 5, 1920. A few days after his return home he became restless at night and up to the present time (nine months) has not slept well at night. According to the description of the mother, he would stay awake at night talking to himself. He generally went to sleep about 4 a. m. and slept until noon. He became very emotional and shy. Shortly after discharge various tic-like movements made their appearance. Thus when he was seen in May he would repeatedly touch his forefinger to his tongue and place the wet finger to his cheek and also on various objects of furniture. He was very nervous and in constant activity. Since his illness his disposition had changed. He was afraid of everybody and had become morose and queer. His memory had become impaired so that he did not remember having been in the hospital. This condition has persisted except that other tic-like movements have followed, replacing the earlier ones, such as licking the back of his hand and wiping his forehead, making beckoning movements with fingers, snapping his

fingers, making circular swinging movements of his arms, going about the room rapping on various articles of furniture, etc. In July he began to spit and when seen was constantly expectorating on the floor so that at the end of an hour there was quite a collection of fluid. His speech became more indistinct and mumbling. When seen December 20, there was no improvement in his condition, he still remained awake and active all night and it was necessary to place him in an institution.

CASE 39.—P. E., a white boy, aged 9½ years, was well until February 11, 1920. On that night he slept poorly. Two days later he had double vision and was at times delirious. Insomnia followed and he was admitted to the Harriet Lane Home February 19, 1920. Examination on admission showed a well-nourished boy, at times rational but at other times threshing about in bed in active delirium. The pupils were dilated but no palsies were made out. The reflexes were active. The leucocyte count was 12,600. The spinal fluid showed 51 cells per c.mm. and gave a positive globulin reaction. The Wassermann test was negative with the blood and spinal fluid. During the periods of delirium the patient made exaggerated uncoördinated movements of the limbs and sedatives were required. The temperature on admission was 101° F. and fell to normal on the fourth day. At this time the delirium and movements had stopped, the patient was mentally clear and co-operative, slept well at night, and the physical examination was entirely negative. He was discharged March 5. Almost immediately after his return home he developed wakefulness at night and a series of tic-like motor phenomena, present both night and day. These consisted in, first, "stretching" motions of the arms, in which the arm was extended and several quick motions made as one does in stretching. A similar movement was made with the legs. When asked why he did this, he said he felt better after the motion had been made. There was no marked pain in the extremities. Second, the forefinger and middle finger were raised to the nose and a wiping movement made, the patient blowing through the nose at the same time. There was no nasal discharge. Third, constant movements of the fingers, as placing the middle finger on the forefinger, the ring finger on the middle finger and the little finger on the ring finger. Fourth, the patient would take a deep breath and make a quick expiration as one does in clearing the throat. However, there was no production of mucus or sputum. The boy talked in a whisper and was very fidgety and excited. Mentally he was clear and there was no return of the delirium. Physical examination was negative. The spinal fluid was normal except for the presence of globulin. He was kept in the hospital several days, and on account of his activity and inability to sleep was transferred to the psychiatric ward. He remained there for several weeks without marked improvement. When seen at home in July these movements were still present and he had developed the habit of spitting. In September the arm motions had stopped but the insomnia had not improved. By the last of October he was sleeping fairly well at night, though waking up frequently. No tic-like movements were observed and he had stopped spitting. However, he was very nervous and excitable, crying easily and extremely fidgety, constantly using his hands to handle objects on the desk, to fumble with his clothing, etc. He was sent to school and has done fairly well.

The characteristic features of these movements are, first, their constant repetition, and second, their short duration. Thus, after one tic-like movement has vanished, another movement or habit spasm appears in its place. These movements are especially marked at night in many instances.

General spasticity as a late symptom or sequel of the disease occasionally associated with a coarse tremor or with choreiform or athetoid movements was present in a number of our cases. There is often a peculiar stiffness of the carriage, the arms, back and shoulders scarcely moving and the steps very short. The face may be expressionless and the voice monotonous, as in Case 2 above.

Hemiathetosis was present in the following case:

CASE 40.—W. S., a white man, aged 29 years, complained of jerking of the left arm and left leg. In February, 1920, the patient had a febrile disease said to be influenza. Following this he was very drowsy and went to sleep while driving or eating. Subsequently there was a period of insomnia. About the middle of April, 1920, the left arm became weak; then the left arm, left leg and left side of the face began to jerk. On examination the patient was mentally clear. There were continuous choreo-athetoid movements of the left arm, left leg and left face without changes in the reflexes or tonicity. The hyperkinetic phenomena were gradually becoming less marked when the patient was last seen (November, 1920).

Paralyses of long duration were rarely observed. In the following instance, however, the paralysis present for many months was rapidly cured by persuasion and was therefore of hysterical origin. In another patient (Case 28) the weakness of the left hand was organic.

CASE 41.—H. H., a colored girl, aged 13 years, stated that in March, 1920, she had measles. On April 1, 1920, she began to have headaches accompanied by nausea and vomiting. She was very drowsy—sleeping constantly for a week. On examination the patient was drowsy and listless and the face was expressionless. There was slight fever. The spinal fluid contained 60 lymphocytes per c.mm. The patient was discharged in June, 1920, apparently well. A week later her right arm became rigid and paralyzed and very tender to the touch. After this condition had persisted for five months, the patient was again admitted to the hospital. The right arm was held rigidly and was very hyperæsthetic. The sensory disturbance was distributed in a "shirt sleeve" area. The condition was believed to be hysterical and was quickly cured by suggestion.

Salivation.—Increased production of saliva and frequent spitting were often observed as late symptoms of the disease in children. One child while being examined would spit to such an extent that there was quite a collection of water on the floor at the end of a half-hour. These children are usually trained by their parents to expectorate into a handkerchief and it was not unusual to see a child coming into the clinic holding a saliva-soaked handkerchief in his hand and constantly spitting into it. In our experience it usually comes on late in convalescence and is frequently more marked at night than in the daytime. At first we were inclined to attribute this habit to the peculiar mental attitude of these children, but it seems more likely that an actual increased production of saliva is present. Netter [71] has called attention to this symptom and makes it the basis of his pilocarpin treatment. Bergé and Hofnagel,[69] Pierre Marie and Levy,[69] and Leahy and Sands [52] report salivation in several cases and Babonneix [70] and Netter [71] acute parotitis (not epidemic) developing in the course of the disease.

It is interesting in this connection to recall Gordon's paper [72] on an epidemic in 1913 of a peculiar malady characterized by enlargement of the salivary glands, salivation, nervous symptoms and spinal fluid changes. The condition, he stated, was not mumps.

Enuresis nocturna was frequently observed in children following recovery from this disease. These children drink a

great deal of water, especially at night during the waking period.

Laboratory Examinations

The leucocyte count according to various authors [15, 68, 58, 73, 74] is usually normal or slightly increased. The average given is between 10,000 and 14,000 per c. mm. The differential formula is usually not altered, unless there is a leucocytosis, and then there is a polymorphonuclear increase.

It should be mentioned that the variability of the leucocyte count may depend somewhat on the stage of the disease when the count is made. The erythrocyte count and the hemoglobin content were not altered in uncomplicated cases. The leucocyte count in our cases varied between 2600 and 20,000. In general, however, the leucocyte count was normal or slightly increased.

Spinal Fluid.—The earlier reports of the disease stated that abnormalities of the cerebrospinal fluid were infrequently observed.[1, 3] Later studies, however, have demonstrated that alterations of the spinal fluid are usually present during the acute stage of the disease. Benard [75] reviewed this subject in 1920 and from his studies and those of other authors [74, 40, 25, 68] the following description of the cerebrospinal fluid in epidemic encephalitis is taken:

(1) The fluid is clear and colorless.

(2) The pressure is normal or slightly increased.

(3) There is a cellular increase early in the disease, which rapidly disappears, although Netter [70] stated that the pleocytosis may reappear during a relapse. The cells are usually mononuclear in type. Polymorphonuclear cells may be present in a small percentage. The total cell count varies from normal to 200 or more per cubic millimeter, averaging from 25 to 40.

(4) The amount of globulin is normal or increased. The increase in the amount of globulin, however, is generally not as marked as the increase in the number of cells ("dissociation cytoalbuminique" (Bernard [75])); an important point in differential diagnosis.

Table I above shows the results of the examinations of the cerebrospinal fluid in our cases. This table brings out the following points:

(1) The fluid from cases during the acute stage of the disease practically always shows some change, either (a) increase in cells, or (b) increase in globulin, or (c) both.

(2) The cell count at the onset may be only slightly increased, rise quickly to a peak and then fall rapidly. For this reason several examinations of the fluid are of more value than a single examination in showing abnormalities, and especially in differentiating from tuberculous meningitis (*v. i.*).

(3) The globulin content is usually only slightly increased except in cases showing evidence of cord involvement; these may show strong globulin reactions. This increase may persist for months after recovery.

(4) The gold chloride curve reveals nothing of special diagnostic value (see Table I).

Urine.—The examination of the urine reveals nothing of diagnostic value. The findings are those of any acute infectious disease.

Bacteriology.—Various observers * have reported the isolation both ante and post mortem of a variety of organisms with which they claim to have reproduced pathologic changes in animals similar to those found in human epidemic encephalitis. These organisms fall into four groups: First, Gram-positive cocci; second, Gram-negative cocci; third, filter-passing globoid bodies, and fourth, a filtrable virus (bacteria-free). If each of these produce similar lesions in animals on intracerebral injection, then one must conclude either that they are all different forms of the same organism, or that the lesions reproduced are non-specific. This uncertainty, together with the negative findings of so many competent observers, make us feel that, although the bacterial nature

* Von Wiessner [78] in 1917 in Vienna isolated a Gram-positive diplostreptococcus with which he produced pathologic changes in animals. This organism was also found by von Economo [55] in the spinal fluid, blood and nasal secretions of patients. Dimitz [25] found the same organism during life and post mortem in cases of the choreiform type of the disease, as did Cohn and Lauber [79] in Munich. The latter were unable to reproduce the disease in animals. Maggiora, Montovani and Tombalato [80] found a small Gram-positive diplococcus, which was agglutinated in a dilution of 1: 100 by the patients' serum and by the serum of convalescents from the disease but not by normal serum. They were able to produce lesions in guinea-pigs on inoculation with cultures of this organism. Maggiore and Sindoni [81] isolated from the blood and spinal fluid of five patients a Gram-negative coccus which on passage through rabbits produced the pathologic picture of encephalitis. They liken these cocci to those isolated by Noguchi in poliomyelitis. Ottolenghi and his co-workers [82] were able to produce pathologic changes in guinea-pigs with a filtrable virus obtained from the blood, spinal fluid and nasal washings. Gabri [83] cultivated an organism (M. tetragenus) from the blood in three cases, but his animal inoculations proved negative. Boccolari and Panini [84] found a Gram-negative diplococcus in the blood. Marinesco [5] in England saw in stained sections Gram-negative diplococci and Gram-positive bacilli, but considered their etiological relationship to the disease open to question. McIntosh and Turnbull [85] and more recently McIntosh [86] obtained positive inoculations in monkeys and rabbits with a virus from the brain of a fatal case, but were unable to grow an organism.

Bradford, Bashford and Wilson [87, 88, 89, 90, 91] recovered from the brains of cases of encephalitis and polyneuritis a filtrable virus, and Basher, Caldwell and Coombie [92] a Gram-positive organism.

In America Stafford [93] and Morse and Crump [94] recovered Gram-positive cocci and the latter succeeded in producing lethargic states in rabbits after intra-cerebral injections. Loewe, Hirschfeld and Strauss [95] isolated a minute filtrable organism from the brain, cerebrospinal fluid and nasal washings, which on injection into rabbits and monkeys produced pathologic changes. Thalheimer [96] recovered a similar organism. House [97] recovered a Gram-positive diplococcus from the brain in a fatal case and Dunn and Heagey [98] a green streptococcus from the blood. Levaditi and Harvier,[99] in France, obtained a filtrable virus from the brain of a fatal case which they claimed reproduced in rabbits typical lesions of epidemic encephalitis. This virus could be passed through several rabbits and then become pathogenic for guinea-pigs. However, the virus was not neutralized by the sera of patients convalescing from the disease. Amoss [100] found that the blood serum of recently convalescent cases of epidemic encephalitis does not neutralize the virus of poliomyelitis, whereas the serum of convalescent cases of poliomyelitis possesses this neutralizing power.

of epidemic encephalitis is highly probable, the causative organism has not yet been definitely demonstrated.

DIAGNOSIS

The clinical features of this disease are so polymorphous that the diagnosis is often particularly difficult even in the presence of an epidemic. At best it is an exclusion diagnosis, for a large number of affections of the nervous system may produce symptom complexes similar to those observed in epidemic encephalitis. Only by elimination of all other known sources of nerve cell damage and by observation over a considerable period of time can the diagnosis be made with any degree of certainty.

The most important diseases which may simulate epidemic encephalitis are the various other types of encephalitis, tuberculous meningitis, abscess and tumor of the brain, acute poliomyelitis and syphilis of the nervous system.

Four types of non-purulent encephalitis are encountered with sufficient frequency to be of importance in differential diagnosis.

(a) Acute non-suppurative encephalitis following the acute infectious diseases such as typhoid fever, measles, mumps, scarlatina and pertussis, is not uncommon, especially in children. In most instances the history of the preceding illness, the presence of numerous convulsions, the short duration and the absence of prolonged lethargy and ocular palsies help in their differentiation. In a few instances the two diseases may be indistinguishable clinically and the diagnosis must rest on the history of the preceding illness. The following case is an example:

CASE 42.—W. E., a white boy, aged 6 years, was taken ill April 18, 1920, with cough, coryza and conjunctivitis. The following day an eruption appeared. The description of this eruption suggested measles. He did fairly well until the night of April 22 when he had several convulsions. He was admitted the following day to the Harriet Lane Home. Examination at this time showed a well-nourished boy, conscious, lying quietly in bed. There was a faded morbilliform eruption over the face, body and extremities. Examination was otherwise negative. Lumbar puncture showed a clear fluid with 130 mononuclear cells per c. mm. and a positive globulin reaction. No tubercle bacilli were found in the fluid. At first the patient seemed dull mentally and the question of tuberculous meningitis was raised. However, the following day the patient was bright and promptly recovered. The spinal fluid on April 27 showed 23 cells and a faintly positive globulin reaction and on May 1 was normal. The child was discharged well the following day. When seen a month later, he seemed to have completely recovered without sequelæ. The diagnosis of an acute encephalitis following measles was made.

(2) *Infantile cerebral paralysis* (*hemiplegia et diplegia spastica infantilis* of Strümpell [172]) is characterized by a sudden onset with fever, convulsions and vomiting and followed by spastic hemiplegia or diplegia often with ocular paralysis and later by athetosis, epilepsy and mental retardation.

(3) The *encephalitic type of acute poliomyelitis* is similar to the disease described above. This type is so rarely observed even during epidemics of acute poliomyelitis (Wickmann,[208] Römer,[169] Peabody, Draper and Dochez [204]) that its relationship to acute poliomyelitis is still questionable.

Typical cases of the two types described above can be differentiated from epidemic encephalitis by the clinical course, the persistence of paralysis and the sequelæ.

(4) *Encephalitis from lead* is occasionally observed in infants.[169] Other evidences of lead poisoning, the history of ingestion of paint and the presence of frequent convulsions usually lead to a positive diagnosis.

Tuberculous Meningitis.—Great difficulty, especially in children, is found in the differentiation of epidemic encephalitis from tuberculous meningitis. Early in the course of either disease the clinical pictures may be so similar that not until several days have elapsed, or until characteristic changes have occurred in the spinal fluid, does the diagnosis become clear.

CASE 43.—E. G. R., a white girl, aged 3½ years, was admitted to the Harriet Lane Home July 17, 1919. Her father had active tuberculosis and there had been intimate contact between the child and the father. The past history had been uneventful. The present illness began suddenly the night of July 13 with vomiting. On the following day the patient vomited again and for the next few days felt tired and weak. July 17, while on a street car, she had a convulsion which was generalized. Following this there were five or six general convulsions. The patient was admitted in a state of stupor with a temperature of 101° F. Physical examination revealed nothing at that time but an unconscious, convulsive child with hyperactive reflexes. The leucocyte count was 13,000 and the spinal fluid practically normal. The tuberculin test was positive. The following day irregular respiration of the Cheyne Stokes type was present and the convulsions continued. Strabismus and a facial weakness developed. The lumbar puncture was repeated on July 19 showing 23 cells per c. mm., a positive globulin reaction and film formation. Subsequent punctures revealed a steady increase in cells (see c. s. f. chart) but no tubercle bacilli could be found. (Guinea-pigs inoculated with the fluid showed no evidence of infection eight weeks later). However, in view of the exposure, positive tuberculin reaction, spinal fluid changes and comatose state with Cheyne Stokes breathing, tuberculous meningitis was considered the most probable diagnosis. The temperature rose on July 23 to 105° F.; following this it fell to normal and remained so. During this period the patient remained in a stuporous state and when aroused was very irritable. On July 27 she began to recognize her surroundings and became less drowsy but extremely irritable. She steadily improved and by the middle of August was walking about the ward apparently normal. She was discharged at this time and reports from the mother indicate complete recovery without sequelæ.

CASE 44.—M. W., a colored girl, aged 2 years, was admitted to the Harriet Lane Home May 20, 1920, with the complaint "sleeps all the time." This condition began the middle of March with trembling of the hands, weakness and unsteadiness in walking. She became less playful, but otherwise nothing abnormal was noted until April 25, when she fell. After this her gait became unsteady, and the tremor of the hands was more noticeable. On May 13 she became very drowsy and following this remained in bed sleeping most of the time. No vomiting, convulsions, or paralyses were noted. Examination on admission showed a well-nourished colored girl lying in a state of deep lethargy from which it was impossible to arouse her. The extremities were somewhat spastic, but the reflexes were not exaggerated. The temperature was normal, the leucocyte count 10,000, the Pirquet and intracutaneous tuberculin reaction with 0.1 mgm. O. T. negative. Lumbar puncture showed a clear fluid, 41 cells per c. mm. and a positive globulin reaction. No films formed in the fluid. The Wassermann test was negative with the blood and spinal fluid. The X-ray picture of the chest showed normal lungs. The

eye-grounds were likewise normal. The diagnosis of epidemic encephalitis was made. On April 22 retraction of the head was noted; the first evidence of meningeal irritation that the patient had shown. This became more marked and on the following day there was opisthotonos. The temperature remained normal. Successive lumbar punctures showed an increase in cells up to 152 with a positive globulin reaction. The patient's condition grew rapidly worse and she died May 24. The question as to diagnosis between epidemic encephalitis and tuberculous meningitis was not settled until autopsy. The development of signs of meningeal irritation and the steady increase in the number of cells with an increasing amount of globulin spoke in favor of the latter, although the absence of fever, the negative tuberculin tests, X-ray examination and inability to demonstrate tubercle bacilli in the spinal fluid were against this diagnosis. Autopsy showed a typical tuberculous meningitis.

There are several points that aid one in this problem, particularly as far as children are concerned:

First. The onset in tuberculous meningitis is more gradual while in encephalitis it is often abrupt and acute, as a rule, resembling the onset of any acute infectious disease.

Second. The temperature in encephalitis is high at the onset, subsiding rather rapidly, whereas in tuberculous meningitis it is not high at onset, but rises toward the end.

Third. Clinical course.—Tuberculous meningitis in children is usually fatal in three weeks, whereas encephalitis may be prolonged over a period of months.

Fourth. Evidence of tuberculosis elsewhere (tuberculosis of the skin, tubercles of the choroid, X-ray of chest, tuberculin reaction).

Fifth. The cerebrospinal fluid.

(a) The pressure is usually normal or very slightly increased in encephalitis, whereas it is usually under increased pressure in tuberculous meningitis.

(b) The cell count in encephalitis may be high at onset, rapidly falling to normal. In tuberculous meningitis, it is not much increased at onset, but rises rapidly as the disease progresses.

(c) The amount of globulin is greater in tuberculous meningitis than in epidemic encephalitis.

(d) Films rarely form in encephalitis in typical manner as in tuberculous meningitis, probably because the amount of globulin and fibrin are less.

(e) Tubercle bacilli may be demonstrated in the films in tuberculous meningitis if repeatedly searched for. Guinea-pig inoculation may be positive.

Poliomyelitis.—In its typical form, poliomyelitis is easily distinguishable from epidemic encephalitis. The nature of the paralyses is entirely different, as are the clinical course and the sequelæ. The chief difficulty lies in the following types of cases:

1. Acute fulminant cases with high fever, great prostration, changes in the spinal fluid and death in a few hours.

Case 45.—D. G., a white girl, aged 6 years, was taken ill on June 18, 1919, with fever and drowsiness. Anorexia developed and she became more lethargic. On June 21 she became unconscious. The fever continued and she was brought to the hospital June 22. Examination on admission showed a somewhat poorly nourished white girl lying in an unconscious state with eyes half closed. The respirations were slow and irregular with periods of apnœa. There was drooling of saliva from the mouth. The deep reflexes were obtained and there was a positive Kernig's sign. The Babinski was positive on the right. The temperature was 101° F.; the leucocyte count was 18,000. Lumbar puncture showed a clear fluid with 55 mononuclear cells per c.mm. and a negative globulin reaction. On the following day the patient had repeated convulsions. The temperature rose rapidly reaching 108° F. She died June 24. No autopsy was performed. In such cases it is impossible to make a differentiation clinically. The presence of an epidemic, however, may be an aid.

2. *The Encephalitic Form of Poliomyelitis.*—This form was discussed briefly above and is extremely rare, even during epidemics of poliomyelitis. One must depend here too on the presence of an epidemic.

We may add that during the period of observation of these cases (1919-1920) poliomyelitis was extremely infrequent in Baltimore. There is no evidence clinically, epidemiologically, or histologically of the identity of the two diseases and one must assume, therefore, that they are distinct entities (see discussion by McNalty[8]).

3. In the form of encephalitis described above (peripheral or polyneuritic type) it may be impossible to differentiate from the same form of poliomyelitis. Symmetrical flaccid paralysis does occur in the latter disease, but it is rare. The occurrence of other cases of encephalitis at the same time, the complete recovery and the optic neuritis in one patient inclined us to regard these cases as encephalitis rather than poliomyelitis.

Syphilis of the central nervous system must always be excluded by the result of the Wassermann test with the blood and cerebrospinal fluid. It is possible for a patient with cerebrospinal syphilis to acquire epidemic encephalitis, but such an occurrence would be unusual. The pupillary changes and the transient pareses always make one think of syphilis. In general, however, the syphilitic diseases of the nervous system are more insidious in their onset and more chronic in their course, and changes in the optic discs are far more common.

Tumor of the Brain.—There is rarely difficulty in differential diagnosis between epidemic encephalitis and tumor of the brain. The former is usually a febrile disease characterized by transient and recurrent paralyses not referable to a single lesion. Moreover, choked disc, so common with intracranial neoplasms, has been rarely observed in instances of epidemic encephalitis. A rapidly growing infiltrating tumor of the pons or mid-brain must be excluded in every instance. A careful study of the sequence of the symptoms, together with repeated examination of the fundi and subarachnoid fluid throughout a period of observation, will usually prevent an error in diagnosis.

Abscess of the Brain.—We have met with one instance in which during life encephalitis was suspected, but at autopsy an abscess of the brain was discovered.

Case 46.—F. M., a colored boy, aged 3½ years, was brought to the Harriet Lane Home September 27, 1920, with the history that he had been well until four weeks ago and since that time had been listless and drowsy, had complained of pains in the abdomen and had vomited after every feeding. There had been no convulsions and the mother did not think there had been fever. Examination on admis-

sion showed a well-nourished colored boy lying in an apathetic state. However, he was quite conscious and apparently understood what was said to him. There were no signs of meningeal irritation, there was slight right facial weakness and the deep reflexes could not be obtained; otherwise the examination was negative. Ophthalmological examination showed a bilateral choked disc. The temperature was normal and remained so during the entire stay in the hospital. The leucocyte count was 14,000. The spinal fluid was under slightly increased pressure with 8 cells per c. mm. and a faintly positive globulin reaction. Epidemic encephalitis was considered, although the bilateral choked disc was evidence against this diagnosis. The patient became more drowsy, he vomited continually and went into coma on September 30. He died the following day. After his death the mother stated that two months before admission the child fell upon a plank, running a nail into his face. This wound healed promptly and the incident was forgotten. Autopsy showed an abscess of the left temporal lobe (staphylococcus aureus) with a punched out hole in the left temporal bone. There was no external evidence of this wound.

The clinical picture of abscess may be very similar to that of encephalitis with an acute onset, high fever, delirium or stupor, slight spinal fluid changes, coma and death. One's suspicions should be excited by the presence of a focus of infection (chronic otitis or mastoiditis or sinusitis) or of an injury or evidence of infection elsewhere in the body as well as by localizing symptoms. Blood cultures may be of value here.

Drug Poisoning.—Attention was called by Hassin and Wien [105] to the similarity of the state resulting from barbital (trional) poisoning to that of encephalitis. Such a condition may perhaps be produced by any hypnotic drug. The history and the absence of change in the spinal fluid should eliminate this source of error.

Typhoid and Other Acute Febrile Diseases.—At the time of onset it may be impossible to determine whether we are dealing with an acute infectious disease with mental and cerebral symptoms or with an encephalitis. This is particularly true in children who so frequently react to acute infections with delirium and psychotic states as well as stupor. The differentiation may be possible only after observing the course of the disease, or the results of the laboratory tests.

Uræmia.—Uræmic states may present a picture closely resembling that of encephalitis and this must be kept constantly in mind. We encountered this difficulty in the following case:

CASE 47.—B. McC., a white girl, aged 4 years, was admitted to the Harriet Lane Home March 28, 1920. She had been well until March 7, at which time she had high fever, was drowsy and complained of headache and pain in the eyes. There was a skin eruption which disappeared in a few days. The child continued to be drowsy and vomited repeatedly. There was fever but no paralysis was noted. On March 15 there was a tremor of both hands and, on the following day, the mother noted a strabismus. That evening the child had a general convulsion which was repeated on the succeeding day whereupon she was admitted to the hospital. Physical examination on admission showed a poorly nourished white girl lying in bed in a stuporous condition from which she could be aroused with difficulty. The respirations were slow and deep and suggestive of hyperpnœa. Otherwise the physical examination was negative. Shortly after admission the patient had a general convulsion. The temperature was 101° F., the leucocyte count 18,000 and the bicarbonate content of the blood serum 14 volumes per cent (Van Slyke). Spinal puncture showed clear fluid under somewhat increased pressure, 2 cells per c. mm. and a faintly positive globulin reaction. The urine was clear, its specific gravity 1018, acid, albumin in large amount, sugar negative, acetone a trace, guaiac negative; microscopically it showed a few white cells but no casts. The Wassermann test was negative with the blood and spinal fluid. The patient was given sodium bicarbonate by gavage. She rapidly became comatose, however, and the convulsions were repeated. The temperature rose rapidly to 105.5° F. and the patient died March 29. Lumbar puncture made post mortem showed 52 mononuclear cells per c. mm. and a positive globulin reaction. The clinical diagnosis was epidemic encephalitis. The anatomical diagnosis was chronic, diffuse nephritis. The brain was entirely normal both in gross and on microscopical examination.

The urine, blood pressure, fundus changes and renal function tests should aid in eliminating this source of error.

Peripheral paralyses due to other causes (lead, arsenic, diphtheria, alcohol, beri-beri, etc.).

Before making a diagnosis of the polyneuritic form of this disease it is necessary to eliminate the other causes of peripheral paralysis by the history and appropriate tests.

PROGNOSIS

The mortality varies within wide limits in the various reports. In Germany it has been 30 to 40 per cent (Economo, Dimitz [25]), in France 25 to 30 per cent (Netter,[3] Bernard [26]), in England 20 to 50 per cent (McNalty,[8] Howell [107]) and in America 10 to 40 per cent (Abrahamson,[28] Boyd,[44] Wegeforth and Ayer [208]).

In our series of 81 cases there were six deaths, a mortality rate of 7.4 per cent. In general, if the patient survives the acute stage of the disease, the prognosis as to life is fairly good; as to complete recovery, however, the prognosis must be reserved owing to the frequency of sequelæ. Relapses are rare, but are said to have a high mortality (Netter).

TREATMENT

1. *General Measures.*—It is important, in the treatment of this disease, to bear in mind that epidemic encephalitis is not an acute disease of short duration, but may last over a period of many months and that convalescence is as a rule slow and tedious because of the frequency of psychic and motor disturbances as described above. Therefore, these patients should be carefully watched and protected over a sufficient period of time following the subsidence of the acute symptoms of the disease to make sure that recovery is complete before permitting them to take up their regular occupations. This becomes extremely difficult when we find that sequelæ may arise months after apparent recovery.

At the onset of symptoms the patient should be placed in a separate room and kept as quiet as possible. Careful supervision is required because of the development of excitation reactions (delirium, mania, chorea, etc.). General isolation of the patient is advisable, but it is not necessary to isolate so strictly as with diseases of more infectious a nature. We know of no disease in which careful nursing plays a more important rôle, for these patients are generally quite helpless.

The diet should be liquid or soft since difficulty in swallowing is often present and gavage may be necessary. One of our patients in deep lethargy had to be fed by gavage for five weeks. Sedatives may be necessary during the state of agitation, delirium and motor excitation. During convalescence, also, the patient should be protected in every way possible and fatigue and excitement avoided. It is a mistake to regard the patients as "cured" after the acute symptoms have subsided, for during convalescence the unpleasant sequelæ, insomnia, psychic disturbances, change in disposition and general motor overactivity, often make their appearance. The parents and relatives should be forewarned of the possibility of the appearance of these symptoms, and parents should be advised not to punish children for odd and untidy acts entirely beyond their control. The insomnia is most difficult to combat. We have had no success with hypnotics, baths or packs, and have allowed the patients to sleep during the daytime, receiving their food when awake. Most of them have improved with time, but great patience on the part of parents and relatives is required. Leahy and Sands advise that these patients be kept awake during the daytime and that occupational therapy be employed.

2. *Drugs.*—There is no specific for this malady, although a variety of drugs have been used. Netter,[109] basing his opinion on the work of Crowe and Cushing, believes that hexamethylenamine is of value when given by mouth. If the urine be carefully watched there is no harm in giving this drug, although its value is problematical. The same author also advises pilocarpin in patients with sialorrhea, believing that in this way one may influence the elimination of the virus. Although sialorrhea was frequently observed in our cases, we have had no experience with the use of sialogogues.

Salvarsan has found favor with various observers (Netter,[109] Fourrier [110]), the latter finding marked improvement following its administration. The specificity of arsenic in these cases is doubtful. Sedatives, as mentioned above, are helpful in the acute stage, although their use in the chronic sleeplessness of convalescence is disappointing.

3. *Intraspinous Therapy.*—Repeated withdrawal of spinal fluid during the acute stage of the disease, especially if the fluid be under increases pressure, is generally regarded as of value. Reasoning by analogy with poliomyelitis Netter,[109] Sabrazes and Massias,[111] Marinesco,[8] Sicard [112] and others advise the intraspinous injection of the blood of convalescent patients, and Cantieri and Vegni [113] the intraspinous injection of the spinal fluid of convalescent patients. The scarcity of available convalescents makes this form of therapy limited, unless one encounters a large local epidemic. It is quite possible that the local irritation produced is the factor of value in this treatment as is probably the case in the improvement after the injection of other sera intraspinously (antitetanic serum Laubie,[114] grippe serum Fendel,[115] etc.).

4. *Miscellaneous.*—Netter [22] has been an exponent of the use of the "abscess of fixation," that is, the production of a sterile abscess by injection of turpentine in a remote part of the body. He reports marked improvement following its use. The injection of various sera (grippe serum Fendel,[115] Oehming,[39] auto-serum Brill,[116] Bourges and Marcandier [117]), the intravenous injection of hypertonic salt solutions (Hoffman [118]) and the injections of colloidal iodin solutions (Claisse [119]) have been recommended. We have had no experience with these measures. We may say, in summary, that there is no specific therapy for this disease. Each case must be treated on its own merits with quiet, rest, hypnotics, careful nursing and feeding and spinal punctures during the acute stage, and careful attention during convalescence. Individual symptoms should be treated symptomatically as they arise.

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FIG. 1.—(Case 2.) A patient with marked lethargy.

FIG. 2.—(Case 2.) Same patient as in Fig. 1, two months later, after disappearance of lethargy. The mask-like facies was still present.

FIG. 3.—Same patient as Figs. 1 and 2, five months later. The face was still mask-like.

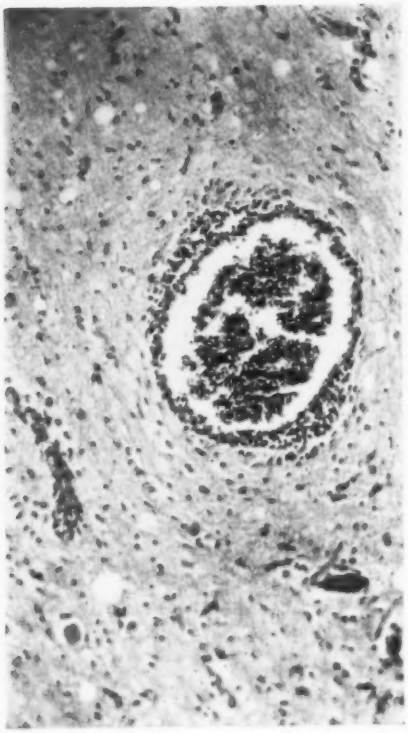

FIG. 4.—(Case 6.) × 146. Marked perivascular round-cell infiltration. Area was in the substantia nigra.

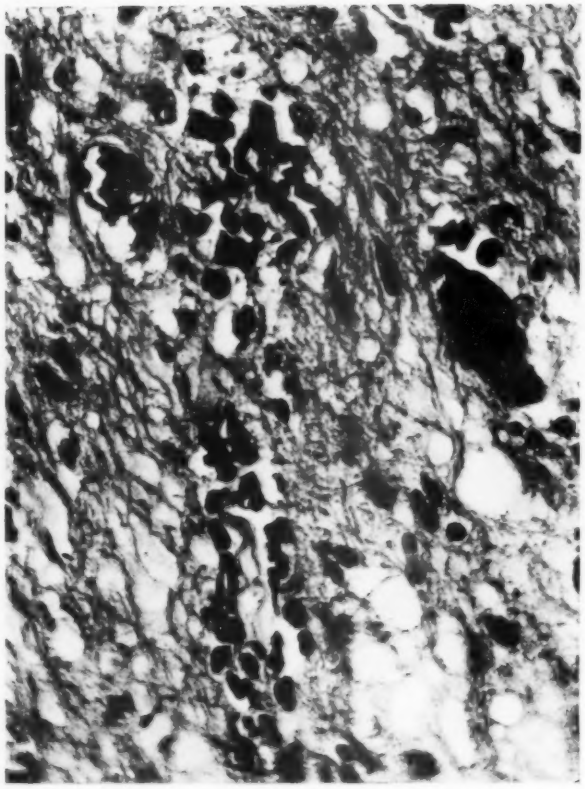

FIG. 5.—(Case 6.) × 480. Hight power of area of substantia nigra to show a collection of round cells near a small blood-vessel.

FIG. 6.—(Case 17.) Bilateral ptosis and mask-like facies in an infant of 7 weeks.

FIG. 7.—(Case 19.) Unilateral ptosis—"ironed-out" face.

FIG. 8.—(Case 29.) Facial expression after subsidence of choreiform movements.

FIG. 9.—(Case 34.) Left facial palsy in epidemic encephalitis.

FIG. 10.—(Case 35.) Expressionless face.

FIG. 11.—(Case 35.) Same patient as in Fig. 10, three months later.

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STUDIES ON EXPERIMENTAL RICKETS

III. A PATHOLOGICAL CONDITION BEARING FUNDAMENTAL RESEMBLANCES TO RICKETS OF THE HUMAN BEING RESULTING FROM DIETS LOW IN PHOSPHORUS AND FAT-SOLUBLE A: THE PHOSPHATE ION IN ITS PREVENTION

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As is now well known, Mellanby [1] has reported the production of rickets in puppies by diets deficient in their content of fat-soluble A,* or an antirachitic factor having a similar distribution. Unfortunately, it has not been possible to evaluate Mellanby's results by reading his published writings, since he has never supplied objective proof of the production of rickets in the form of illustrations showing the appearance of his specimens through the microscope. This omission has been unfortunate, inasmuch as the diagnosis of this disease can be made with certainty only on the evidence derived from microscopic changes in the bones. The gross deformities which characterize rickets can be simulated in other pathological conditions, as, for example, the osteoporosis which develops in growing puppies during confinement in small cages. Evidence afforded by the X-ray is not completely convincing. X-ray examination fails to disclose the exact nature of the pathological process in operation, and to differentiate rickets, as it commonly occurs in children, from related conditions such as can be produced in animals through dietetic influence.

In a previous publication [2] we described 11 diets, some of which produced gross deformities resembling those seen in rickets. The nature of the faults of these diets was in all cases clearly pointed out. These diets included formulæ for food mixtures in which there was a deficiency of but one dietary factor, *i. e.*, calcium or fat-soluble A. The other diets described were faulty in the following respects: lack of fat-soluble A and excess of calcium, and low calcium and low fat-soluble A. Since the preparation of the earlier paper we have had occasion to observe also the effect of changing the plane of intake of the phosphate ion on the growing bone.

* We are using provisionally the term fat-soluble A, to designate the organic factor which may play a special rôle in bone development. In a later paper we shall present further experimental data, of a nature which will serve better than those contained in the present discussion for deciding whether the organic factor contained in cod-liver oil, to which that substance owes its therapeutic value in certain diseases affecting the skeleton, is identical with the factor which we here refer to as fat-soluble A.

Experiments Designed to Show the Effects on the Skeleton of Diets Low in Their Content of Fat-Soluble A and Phosphorus

In order to bring out the effects of varying the plane of the phosphate ion in the diet on bone development, we have employed the following food mixtures:

Diet of Lot 2667

Rolled oats	40.0
Flaxseed meal	8.3
Sodium chloride	1.0
Calcium carbonate	1.5
Dextrin	49.2

100 gms. of this mixture contained 0.6714 gms. of calcium and 0.2165 gms. of phosphorus.

This diet is deficient to some extent in its protein content. The protein, both in amount and quality, is adequate, however, to induce growth, though at a rate distinctly below the maximum. But no development is possible on this food mixture unless it is supplemented by some substance which will serve as a source of the factor, fat-soluble A. This diet, as stated, is deficient in fat-soluble A, and also contains a relatively small amount of phosphorus.

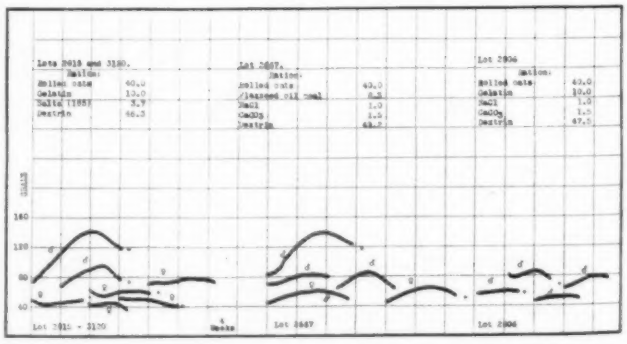

Chart I.

The Curves in this Chart Illustrate the Weight Changes in Young Rats Fed the Diets Described in the Text.

When young rats weighing from 20 to 70 gms. between 18 and 50 days old are confined to this diet, without the addition

of any substance supplying fat-soluble A, they soon cease to increase in weight and then rapidly decline (Chart I). After an interval which varies markedly, depending principally on the age of the animal but to some extent on individual resistance, they all develop xerophthalmia. In our extensive experience no animal has ever recovered from this condition unless a substance capable of acting as a source of fat-soluble A was added to its diet. On the addition of such a substance, *e. g.*, butter fat or cod-liver oil, animals suffering from xerophthalmia steadily improve and return to normal health. While recovery is taking place, growth is resumed. With this diet we have conducted scores of experiments; the general behavior of the animals placed upon it and the development of xerophthalmia have occurred with unvarying regularity as described.

DIET OF LOT 2806

Rolled oats	40.0
Gelatin	10.0
Sodium chloride	1.0
Calcium carbonate	1.5
Dextrin	47.5

100 gms. of this mixture contained 0.6414 gms. of calcium and 0.1580 gms. of phosphorus.

This diet contains protein of good quality and in sufficient amount to enable young rats to grow at a fairly rapid rate, provided the faults in the diet are corrected by suitable additions. The principal defect in this diet is a deficiency in fat-soluble A. Without the addition of this factor no growth is possible, and severe xerophthalmia develops followed by death. A second defect in the diet sufficiently grave to interfere in a measure with growth is the lack of sufficient phosphate ion. While growth can take place on the formula tabulated above, supplemented with some substance acting as a source of fat-soluble A, it is not so satisfactory as when the sodium chloride and calcium carbonate are replaced by a salt mixture containing not only these substances but suitable amounts of the phosphate ion as well.

Methods.—All the animals in the experiments were killed with ether. After careful postmortem examination various bones and some of the soft tissues were saved for histological examination.

In preparing bones for microscopical examination we have usually used the method recommended by Pommer—decalcification in Müller's fluid for periods ranging from two to fourteen days after preliminary fixation in formalin. The bones were dehydrated, embedded in celloidin and the blocks cut into sections from 10 to 60 microns thick. While we have used thionin and other dyes and have treated a large number of sections with silver nitrate after the method of Von Kossa, no staining technique has proved to be so satisfactory as that in which a combination of Ehrlich's hæmatoxylin with water soluble eosin is used. We have controlled the material which was partially decalcified in Müller's fluid by means of celloidin and frozen sections of undecalcified bones.

The Pathological Condition Produced in the Skeleton by the Administration of Diets Deficient in their Content of Fat-Soluble A and Phosphorus.—The diets described above (diets of lots 2667 and 2806) give rise to pathological pictures in the bone presenting a wide range of variation. At one extreme, the picture closely resembles that of rickets as that disease manifests itself in the human being, at the other extreme, osteoporosis.

The autopsy findings in the rats whose condition most closely resembled rickets, were as follows: The animals were undernourished and under-developed. Their coats were rough and uneven. Xerophthalmia was invariably present. The teeth were loose; the incisor teeth were easily fractured or extracted. In some animals spontaneous fracture of one of the incisors had occurred. The cranial bones were soft. The costochondral junctions were enlarged and the oval swellings formed were unusually long. In some rats there was moderate displacement inwards of the middle tier of costochondral junctions. In some animals a few fractures of the ribs marked by callous formation but without deformity of the costal arch were present. The spleen was atrophic in some animals, in others more or less enlarged. The thymus was atrophic. There was little or no fat. The long bones were straight and were not factured. The ends of the long bones were greatly enlarged. The femur and tibia were easily cut and gave little evidence of the presence of calcium salts until the knife had entered well into the shaft. Gross examination of the cut surface revealed a broad zone of a pale tissue, 2-4 mm. in width, lying between the epiphyseal cartilage and the shaft (the rachitic metaphysis).

The epiphyseal cartilage in some animals was increased in width throughout the entire area of the section. It was more common, however, to find it of a normal width or a width not greatly exceeding the normal except at the periphery of the bone. At the periphery prolongations of cartilage extended diaphysealwards well into the metaphysis. Higher magnification showed the matrix of the cartilage to be unusually abundant in proportion to the numbers of cells present. The undifferentiated portion of epiphyseal cartilage was represented by a thin zone in which the cells appeared to be unusually far apart. The proliferative zone contained columns of cells aggregated in bullet-shaped masses, the points of which were directed toward the undifferentiated cartilage. Each bullet-shaped mass was separated from its fellows by a broad band of matrix (Fig. 3). As the metaphysis was approached, the cells of the proliferative zone, which were small and often flattened, with lense-shaped nuclei, grew larger and assumed a nearly spherical form, and at the same time underwent a progressive loss of affinity for the basic dyes. The nuclei became larger and the staining reaction approached more nearly that of the osteoid tissue in the metaphysis (Fig. 4). At the points of junction of the cartilage with the metaphysis the cartilage cells lost their columnar arrangement and became heaped together in disorderly masses. There was no evidence of calcium deposition in the zone of proliferative cartilage corresponding to the zone of provisional calcification in the normal bone, or else the calcification was fragmentary. The cartilage was invaded to a considerable extent by blood vessels from the marrow cavity, but did not appear to be greatly disorganized. The invading vessels for the most part were slender and appeared to advance, in some instances at least, along the strands of matrix between the columns of cells.

The metaphysis was composed chiefly of osteoid trabeculæ but also of blood vessels carrying with them marrow elements, tongue-like bands of cartilage cells of various thicknesses continuous with the epiphyseal cartilage and of islands of cartilage cells. The trabeculæ were broad. Many of them contained central cores of uncalcified cartilage and in almost all of them single cartilage cells could be identified or small groups in various stages of transition to a state indistinguishable from the cells of the osteoid itself. The trabeculæ were separated from each other by wide blood channels each of which was surrounded by a small amount of delicate connective tissue and a few marrow elements. The osteoblasts covering the trabeculæ were flattened, spread out like endothelial cells and had small nuclei. The osteoid of the trabeculæ was for the most part laid down in the form of lamellæ, but the lamellar arrangement could not always be made out. The bone corpuscles varied in size, but by far the majority were, to judge from their nuclei, small cells. The large prolongations of the epiphyseal cartilage into the metaphysis seemed to retain for the greater part of their extent the normal staining reaction to hæmatoxylin (Fig. 4). The smaller prolongations, those consisting of thin strands of cartilage cells, and the

terminal portions of the large prolongations just alluded to, seemed to lose their staining reaction almost entirely. The loss of the staining reaction appeared to occur in the neighborhood of the blood vessels and apparently depended on the intimacy of contact between the cartilage cells and the vascular elements. It was most marked in the strands or groups of cartilage cells which had become incorporated in the interior of the osteoid trabeculæ. As the cartilage cells came into close relationship with the marrow elements, they also appeared to undergo changes in their morphology. The cell bodies became smaller and took on a vesicular appearance. Around the cell body there developed a homogeneous material having the same staining reactions and outward appearance as the uncalcified material formed by the osteoblasts. In the osteoid trabeculæ removed some distance from the epiphyseal cartilage, where the change taking place in the cartilage cells appeared to be far advanced, the cartilage cells were so reduced in size that they could be distinguished from the osteoblasts only by their oval cell capsule and the vesicular appearance of the cytoplasm, or could be differentiated with the greatest difficulty or not at all. In some osteoid trabeculæ cartilage cells could be found in all stages of transition to osteoblasts.* The cartilage cells embedded in the osteoid trabeculæ seemed to be stimulated to reproductive activity, for areas were seen where single cells had obviously given rise to from two to five daughter cells (Fig. 5). Cell division was apparently accomplished by amitosis. The cartilage cells composing the small islands in the metaphysis underwent the changes just enumerated. The cartilage cells composing the larger islands, however, retained their ordinary staining reactions except at the periphery where an abrupt change to osteoid took place. These large islands of cartilage cells appeared to be insulated by thin rims of osteoid. It is important to note that the tendency toward calcium deposition must have been very marked even in those animals that exhibited the pronounced changes of a rachitic nature just enumerated, for in the bones of the great majority of them linear deposits of lime salts were found which passed transversely across the metaphysis at right angles to the long axis of the bone. These deposits were sharply separated from the shaft of the bone, on the one hand, and from the proliferative zone of cartilage on the other. In some animals a single bone showed two or three of these evidences of abortive attempts at healing (Figs. 8 and 9). Such bones were striking in their resemblance to the bones of children showing the lesions of so-called "healing rickets."

In the shaft of the bones of the animals showing extreme changes of the nature just described, the formation of osteoid tissue about the trabeculæ was markedly increased (Fig. 6). The small trabeculæ of calcified bone were completely surrounded by broad areas of osteoid and the periosteum was widely separated from the cortex by masses of osteoid tissue (Fig. 7). New bone formation in fibrous tissue was found occasionally beneath the periosteum in the region of the metaphysis. The osteoid tissue on the periosteal side of the cortex was traversed by numerous blood vessels. Here and there it was possible to find evidences of bone resorption. The evidences of resorptive activity in the metaphysis were very slight.

In animals at the other extreme the abnormality was of the nature of an osteoporosis. The epiphyseal cartilages were perhaps slightly irregular, but they were narrow. There was no evidence of abnormal persistence of the cartilage cells. Heavy continuous deposits of lime salts were present in the diaphyseal border of the cartilage, and this latter terminated abruptly in contact with the shaft. The marrow cavity was crowded with hæmatopoietic cells. The cortex was thin but completely calcified. In the medullary cavities of some bones a few very thin, completely calcified trabeculæ were present, but in others the only bone to be found was the cortex of the shaft. In some of the rats showing these extreme osteoporotic changes the trabeculæ were invested with fibrous tissue and around them were to be found basophile cells with single nuclei and large granules. The evidences of resorptive activity in the trabeculæ were well marked. No osteoid was present anywhere. The gross *autopsy findings* in these animals were in accord with the picture which the microscope revealed in the sections. There were no deformities of the skeleton of any sort, but the bones were abnormally slender, a finding especially noticeable in the ribs, because of the contrast between the thin shaft and the costal cartilages. The latter appeared to be of normal size or even larger than normal. The bones gave evidence of the presence of calcium salts when an attempt was made to cut them; they were brittle and fragile, although there were no fractures to be found.

All stages of transition were found between the two extremes of the pathological process induced in the skeleton by the diets low in fat-soluble A and phosphorus, and by far the greater number of the animals examined may be said to have exhibited pathological changes of a mixed nature. In all these animals of the intermediary group the pathological picture presented had a rachitic background. The deposition of the calcium salts in the cartilages was irregular, and areas were found in the proliferative zone in which lime salt deposits were not present. The cartilages in most of the rats were extremely irregular, and in a considerable number of animals there was persistence of the cartilage with the formation of a thick proliferative zone (Fig. 10). In this thick proliferative zone large defects were noted due to invasion of the cartilage by blood vessels. In some of the animals, although calcification of the cartilage had occurred, prolongation of the cartilage was pronounced. Other animals showed cartilage cells in calcified as well as uncalcified portions undergoing the changes already alluded to which have been probably wrongly regarded as signs of degeneration. In almost all the rats showing these mixed lesions there was a narrow metaphysis or a partial metaphysis, *i. e.*, one extending part way across the bone. All the changes characteristic of rickets in the human being were present with the exception of the absence of calcium deposition in the proliferative cartilage. The number of trabeculæ in the shaft, however, was greatly reduced and, while even broad zones of osteoid were in evidence about the trabeculæ, there were many signs that the trabeculæ were in process of resorption and were being removed from the medullary cavity (Fig. 11). The gross changes in the skeleton consisted merely in varying degrees of enlargement of the costochondral junctions and the ends of the long bones of the extremities.

Experiments Designed to Show the Effects on the Skeleton of Diets Low in Their Content of Fat-Soluble A, But Having an Adequate Amount of Phosphorus

Diets of Lots 3120 and 2815

Rolled oats	40.0
Gelatin	10.0
Salts (185)*	3.7
Dextrin	46.3

100 grams of this mixture contained 0.3150 gms. of calcium, and 0.5383 gms. of phosphorus.

* Composition of salt mixture 185.

* The disappearance of the staining reaction of the cartilage cells and the morphological changes enumerated do not indicate a degenerative process. On the contrary, the existence of the cartilage cells appeared to be prolonged in a remarkable manner. As the cartilage was invaded by the capillaries, its cells became embedded in osteoid through the activity of the osteoblasts. In this envelopment of osteoid they persisted and became indistinguishable from the cells of the osteoid investment. Our experience would lead us to believe that the cartilage cells may undergo metaplasia into the cells of the osteoid.

NaCl	0.173
$MgSO_4$ (anhydr)	0.266
$NaH_2PO_4 + H_2O$	0.347
K_2HPO_4	0.954
$CaH_4(PO_4)_2 + H_2O$	0.540
Fe citrate	0.118
Ca lactate	1.300

Of this mixture 3.7 gms. were added to every 100 gms. of ration.

This diet, as is easily seen, contains protein of fairly satisfactory amount and quality. The properties of the mixture differ from those of the diets of Lots 2806 and 2667 in that there is contained a salt mixture having among other things the sodium, chlorine, calcium and phosphate ions in satisfactory amounts. The diets of Lots 2806 and 2667, however, lacked the phosphate ion from among the necessary supplements for the inorganic moiety of this diet. When young rats are restricted to this diet they soon fail to increase in weight and then slowly decline. They invariably develop xerophthalmia and die. This diet supplemented with some substance acting as a source of fat-soluble A induces growth and apparently fairly satisfactory nutrition over a considerable period.

The Pathological Conditions Produced in the Skeleton by Administration of the Diet Deficient in its Content of Fat-Soluble A, but Containing an Adequate Amount of Phosphorus

The eleven rats fed on this diet were all small and exceedingly mal-nourished. The eyes showed the characteristic xerophthalmia. The incisor teeth were fragile, loose in their sockets, and in some animals fractured. On removal of the skin there was a notable absence of fat. The thorax externally showed no deformity. On opening the thorax the arch of the ribs and cartilages was normal and there was no deformity or enlargement of the costo-chondral junctions. The shafts of the ribs appeared extremely thin, and the costal cartilages large as compared with them. No fractures of the ribs were present. The vertebral column was not bent. Both thymus and spleen were atrophic. The fore and hind legs were slender, but presented no deformities, fractures, or enlargements of the ends of the long bones. On section of the femur and tibia the resistance was greatly diminished, but the bones grated under the knife as the latter entered the shaft. On examination of the cut surface the cortex was found to be exceedingly thin. The marrow cavity extended close to or actually to the cartilage. There was either no sub-chondral zone of spongiosa, or an exceedingly thin one. The epiphyseal cartilage separating the large nucleus of ossification from the shaft appeared as a narrow band, the width of which was everywhere equal. By means of the binocular microscope there could be detected a continuous thin line of calcium deposit along the diaphyseal border of the cartilage.

On microscopic examination the results of gross examination were corroborated. The band of epiphyseal cartilage was found to be exceedingly narrow, and the columns of cartilage cells correspondingly short. Calcification of the proliferative zone lying in contact with the marrow cavity was complete. The character of the calcification corresponded closely to that found in the bones of animals whose growth is approaching completion, that is, each cell was completely enveloped by calcium deposit. The diaphyseal portion of the bone also had in some respects the appearance which characterizes the bones of animals whose growth has almost ceased, that is, there were few trabeculæ immediately adjacent to the cartilage; in some of the animals there were none (Fig. 12). When trabeculæ were present they were most numerous at the periphery, filling in the angles between the epiphyseal cartilage and the cortex. In the central portion of the bone in all the rats the marrow cavity was in immediate contact with the epiphyseal cartilage. The trabeculæ themselves were thin. In most of the rats they showed no osteoid borders anywhere. In some animals, however, the trabeculæ here and there were partially covered with borders of osteoid, some of which slightly exceeded the normal in thickness. The cortex was thin, completely calcified, and solid, *i. e.*, it did not contain spongy tissue. In the bones of the majority of the animals the signs of resorption were well marked. The trabeculæ were invested with layers of fibrous tissue, and in the periphery of the trabeculæ were countless numbers of rather large mononuclear cells conspicuous for the presence of basophilic granulations. These cells were thought to be connected with the resorptive process. In many trabeculæ holes and cavities could be found in which osteoblasts could be identified lying free, and in other places osteoblasts could be seen lying half in the calcified part of the trabeculæ and half in the osteoid border. Where osteoid borders were present, they appeared in the preparations stained with hæmotoxylin-eosin to be exceedingly pale, almost translucent, and the cell bodies of the osteoblasts in them, apparently strongly basophilic, were clearly defined in contrast. The osteoblasts themselves were large and in the trabeculæ appeared unusually close together. The nuclei were large and in those cells lying in the osteoid (where the cell bodies could be studied) were eccentrically placed in the cell body. The cell body was not round but irregularly oval. Near the nucleus at about the center of the cell was a large, round area of vacuolization about the size of the nucleus. It was by means of this area of vacuolization that the osteoblasts lying free in the holes in the trabeculæ or along the sides could be identified with such certainty. Many of the trabeculæ were covered with large numbers of osteoblasts. We are inclined to believe that the osteoid borders were caused not by growth but by removal of the lime salts, *i. e.*, halisteresis. The marrow, with the exceptions already noted, was normal. The basophilic cells which surrounded the trabeculæ were in no instance found in the marrow cavity.

Discussion

The first two diets used in these experiments (diets of lots 2667 and 2806) characterized by a deficiency in fat-soluble A and phosphorus, produced, as anticipated, xerophthalmia and changes in the skeleton. The xerophthalmia, as nearly as we could judge from gross inspection of the eyes, did not vary except in degree. The changes in the skeleton, however, exhibited a wide range of variation. In the animals at one extreme (in 13 rats) the ends of the long bones were characteristically large. The zone of proliferative cartilage in places was greatly broadened and continued in long processes toward the shaft. The cartilage cells in these processes and those elsewhere in contact with the marrow elements of the metaphysis exhibited the characteristic morphological changes and loss of staining properties so commonly seen in the rickets of human beings. The metaphysis itself was broad and composed, in addition to the vascular elements, almost entirely of osteoid trabeculæ. Calcification of the zone of the proliferative cartilage, corresponding to the provisional zone in the normal bone, was either entirely absent or very deficient. In almost all instances, however, there were broken linear deposits of calcium in the metaphysis, extending across it at right angles to the long axis of the bone. The pathological condition in these animals, showing the more extreme changes, exhibited all the fundamental characteristics of rickets, as it manifests itself in human beings, and may be said to have

borne a strong resemblance to a certain form of rickets occurring in the human being, characterized pathologically by linear zones of lime salt deposition in the metaphysis, indicating alternate healing and exacerbation.

In the animals at the other extreme (in 9 rats) the pathological condition corresponded to what is ordinarily included under the term osteoporosis. The epiphyseal cartilage was reduced to a narrow band. The transition between cartilage and shaft was abrupt. Calcification of the cartilage was regular and complete. The few thin trabeculæ were free from osteoid, and resorptive phenomena were abundantly in evidence. The pathological condition of the bones exhibited by the rats at this extreme of the series showed no evidences of rickets whatsoever, but on the contrary complete calcification of all elements both cartilage and trabeculæ.

The majority of the animals on these two faulty diets (27 rats), however, showed pathological conditions in the skeleton intermediary between the two extremes just briefly outlined. The trabeculæ were bordered with osteoid, not the thin border present in growing young animals, but broad zones comparable to those seen in the advanced rickets of children or even exceeding them in thickness. In all there was irregularity and broadening of the epiphyseal cartilage and defects in its calcification, in some instances most extensive, in others small. Some animals showed short metaphyses or partial metaphyses, in which were columns or masses of cartilage in an uncalcified or in an incompletely calcified state, displaying the morphological changes and alterations in staining reactions previously enumerated. The number of the trabeculæ were few, and in the trabeculæ, in particular those close to the cartilage, there were present abundant evidences of resorptive activity. The pathological conditions displayed in the bones of the rats showing these intermediary changes bore a marked resemblance to the not very advanced rachitis of human beings, when the healing process has been well established or has progressed far toward completion. An anomalous condition was present characterized by abundant calcium deposits in the cartilage on the one hand, and borders of the trabeculæ still uncalcified on the other, a well recognized and characteristic intermediary stage in the healing of the rachitis in human beings.

It is not possible to explain why all the rats fed the diets deficient in fat-soluble A and phosphorus failed to develop exactly the same changes in the bone. It is possible that the diets in question were not absolutely constant in their composition, not as regards a deficiency in fat-soluble A—for all the rats without exception developed xerophthalmia—but as regards some other substance. The stock supplies of flaxseed meal and rolled oats were replenished during the course of the experiments several times, and may have been derived from different sources.* A reason for suspecting that variations in the composition of the diets may have had some influence is that the animals which most consistently developed the marked rickets-like changes were the first animals of the series (those of the experiments completed before May 19, 1920). Another explanation, however, must be considered. As already pointed out, there were noted in all the animals, even in those showing the most marked rachitic-like changes, evidences of a strong tendency toward healing, manifesting itself in the deposition of calcium salts in the cartilage. In a large proportion of the animals the healing process, as measured by the extent of calcium deposition in the cartilage, appeared to be far advanced. If the composition of the diets was essentially constant, it is necessary to suppose that the abnormal conditions in the body induced by them, under which lime salts could *not* be taken up by the cartilage and the bone, were not very far removed from other conditions more nearly approaching the normal under which lime salts *could* be taken up by the cartilage and the bone, and that the former state could be transformed into the latter by slight changes in the animals' metabolism. In other words, the particular abnormal equilibrium of the forces concerned with calcification and ossification produced by the faulty diets was unstable. With the rapid decline in the nutrition of the animals occurring during the latter part of the experiments and the corresponding loss in weight, a complete cessation, or at least a great retardation in the rate of growth of the skeleton must have occurred. There must have come about, therefore, a diminished requirement for those substances essential to ossification and calcification, which were insufficiently supplied in the diets. Moreover, it seems probable that a supply of those substances may have been liberated from the tissues of the animals themselves, for example, as the result of the resorptive processes in operation in the bones. From a theoretical standpoint, therefore, it seems possible to think that the processes in operation in the animal leading to the development of the state of extreme malnutrition may have been instrumental in restoring to the organism conditions under which calcium deposition in the skeleton again became possible. For the development of rickets growth is necessary. If the deficiencies in the diet are of such a nature as to render growth of the skeleton impossible, rickets cannot develop. If growth were brought to an end in an animal already rendered rachitic through the administration of faulty diets, there is reason to expect that the rachitic lesion would disappear and a condition of osteoporosis develop. Whatever may have been the cause of the development of pathological changes in the skeleton, from the morphological standpoint, apparently so far removed from each other, there can be no doubt that the osteoporosis exhibited by some of the animals of the series was closely related to the healing process in evidence in the others, and represented merely the healing process in its completed state.

The pathological condition produced in the rat by the diet low in fat-soluble A but containing a complete salt mixture (the diet of Lots 3120 and 2185) were absolutely constant and offered no difficulties of interpretation. In the entire series of eleven animals on this diet the band of proliferative cartilage was narrow, the junction between cartilage and shaft abrupt

* The content of the diets in calcium and phosphorus was calculated from the average composition of rolled oats and flaxseed meal, as compiled by Forbes, Sherman and others, and from the composition of the salt mixtures employed.

FIG. 1.

FIG. 2.

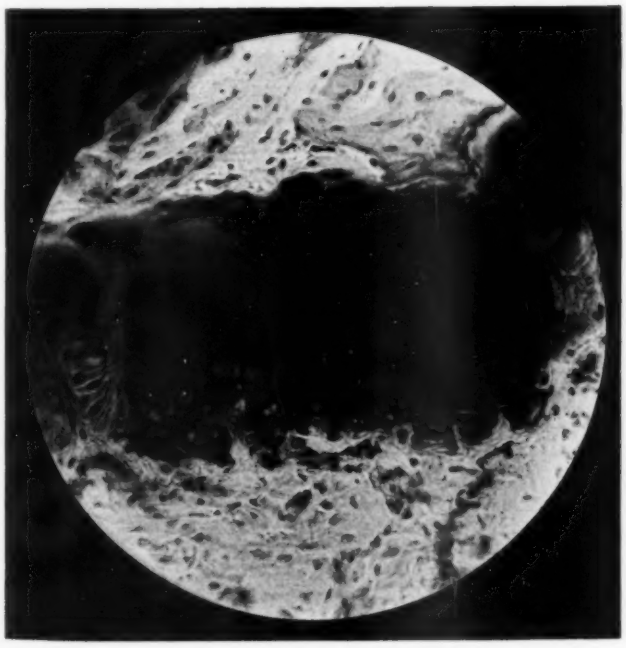

FIG. 3.

FIG. 4.

FIG. 5.

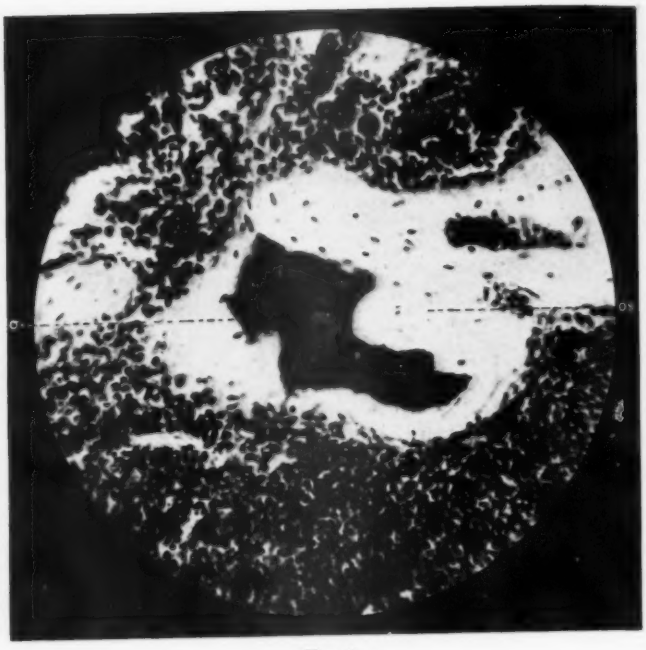

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

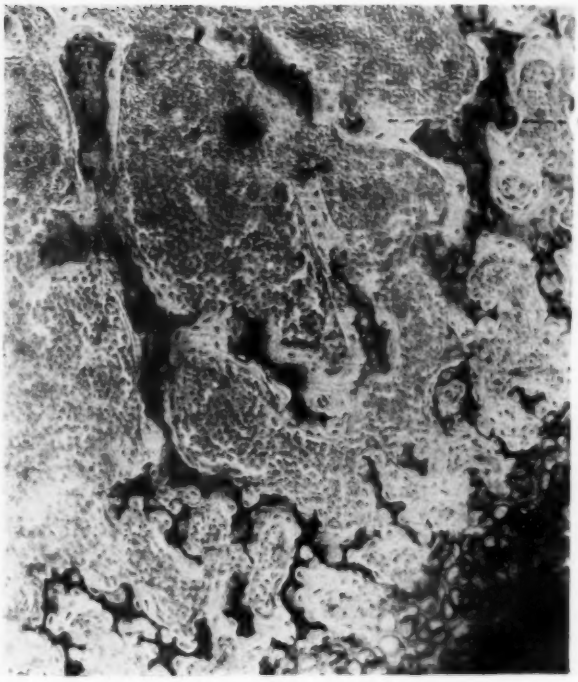

FIG. 11.

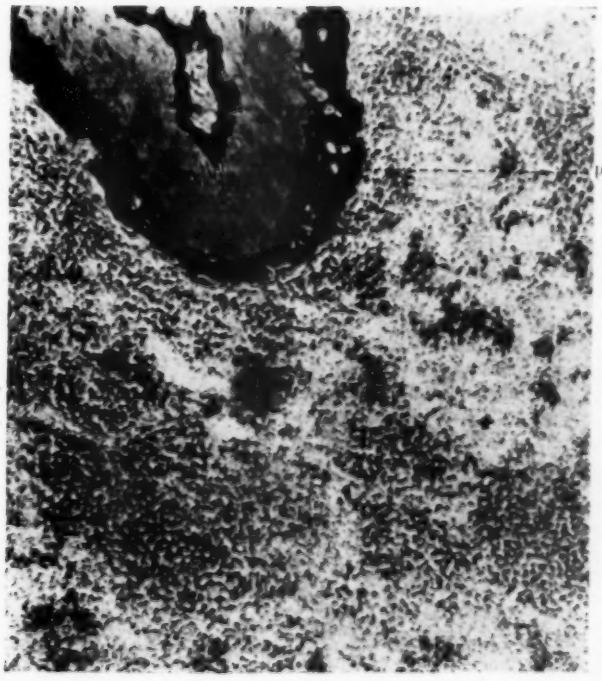

FIG. 12.

and even, the calcification of the cartilage heavy and everywhere complete, the trabeculæ thin; osteoid was not present at all, or was not in greater amount than could be accounted for by the resorptive processes, obviously in operation. The pathological condition induced in the group of rats fed this diet, deficient fat-soluble A, but containing the adequate amount of phosphorus, therefore bore no resemblance whatsoever to rickets. It showed the typical picture of osteoporosis.

The experiments recorded leave no doubt that the two diets having the known deficiencies in fat-soluble A and phosphate may produce in the bone of the rat changes having fundamental resemblance to the pathological changes in the bone which characterize rickets in the human being. At the same time they indicate that the addition of a salt mixture relatively high in its content of the phosphate ion completely prevents the development in the bone of the rat of changes resembling rickets, though it fails to exercise any preventive influence on the development of the xerophthalmia. It seems possible to infer from our experiments, therefore, that the development of rachitic-like changes in the rat induced by diets deficient in fat-soluble A and the phosphate ion can be prevented by the addition to the diet of phosphate-containing salts; and that conversely, for rachitic changes to develop in the presence of a deficiency of fat-soluble A in the diet, the diet in other respects being optimal, a low content of the phosphate ion is essential. The experiments indicate further that in the production of rickets-like conditions in the rat, fat-soluble A cannot be the sole factor concerned. Since the variable in the diets used in these experiments was certain phosphate-containing salts, it might seem possible to infer that it is necessary to consider only the inorganic content of the diet as active, and that a fat-soluble organic factor might be excluded from consideration. Even if it were granted that the induction of the rickets-like changes in the bone results from a disturbance in the level of the body's phosphate, it does not by any means follow that the inorganic ions are the only factors involved. Recent experiments in feeding cod-liver oil, which is known to be high in fat-soluble A but free from phosphate, to rats already rendered rachitic by means of the diet, have proven that an organic substance (cod-liver oil) may exert a powerful influence in causing lime salts to be deposited in the cartilage.[2] Studies on the effects of feeding cod-liver oil to rachitic children have led to similar conclusions.[1] Moreover, Howland and Kramer * have shown that the blood phosphate is low in the blood plasma of rachitic children, and that the administration of cod-liver oil causes a marked rise. It seems not unlikely that a similar result may be accomplished in rats by feeding a diet high in phosphate, and from present knowledge it seems reasonable to suppose that, while the calcification of the bones of children and animals fed diets high in their content of phosphate may be dependent on the elevation of the phosphate level in the blood, the phosphate curve may also be affected by the amount of the organic factor available for the body needs.

* Personal communication.

Finally, our experiments show beyond doubt that the addition of certain phosphorus-containing salts to the diet low in fat-soluble A in no wise prevents the development of xerophthalmia and indicates, as clinical observation has made it necessary to infer, that xerophthalmia and rickets cannot possibly have an identical etiology.

CONCLUSIONS

1. The two diets which were low in their content of fat-soluble A and phosphorus (diets of lots 2667 and 2806) produced in the majority of the young rats placed upon them pathological conditions of the skeleton having a fundamental resemblance to rickets. The pathological conditions produced are not identical, however, with that disease as it usually manifests itself in the human being.

2. The chief difference consisted in the presence of scattered or irregular deposits of calcium salts in the cartilage and metaphysis. The pictures bore a marked resemblance to those seen in rachitic children in whose bones incomplete healing has taken place.

3. When the deficiency in phosphorus is compensated for by the addition of a complete salt mixture containing the phosphate ion (diet of Lots 3120 and 2815), the deficiency in fat-soluble A still existing, no pathological changes of a rachitic nature developed. The addition of the phosphate ion to the diets deficient in it and in the organic factor prevented, therefore, the development of any changes of a rickets-like nature.

4. The experiments reported are not sufficiently numerous or comprehensive to permit of generalizations concerning the effects of a deficiencies of the fat-soluble A and phosphorus or of the fat-soluble A alone. The implication of the experiments is, however, plain.

(a) The phosphate ion in the diet may be a determining influence for or against the development of rickets.

(b) If the phosphate content of the diet is sufficiently high a deficiency of fat-soluble A cannot cause rickets-like changes in the skeleton.

(c) A deficiency in fat-soluble A cannot be the sole cause of rickets. Conversely, it is necessary that the diet be low in its content of phosphorus, all other factors, except fat-soluble A, being optimal for rickets-like conditions to develop.

5. Since the addition of the phosphate ion to the diet prevented the development of the rickets-like changes in the skeleton, but had no effect in preventing xerophthalmia, it seems permissible to infer that xerophthalmia and rickets do not have an identical etiology.

6. The above results do not in our opinion exclude the fat-soluble A from consideration as an etiological factor in the production of rickets and kindred diseases, since the level of the blood phosphate is, in all probability, determined in part by the amount of the fat-soluble A available for the needs of the organism.

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DESCRIPTION OF PLATES

Fig. 1.—Microphotograph showing advanced rickets-like changes in the lower end of the left femur. The picture shows the relative positions of the epiphyseal nucleus (e. n.), cartilage (c), the metaphysis (Met.) and the diaphysis (d) of the bone. The epiphyseal cartilage is persistent at the periphery of the bone.

Fig. 2.—Microphotograph of the lower end of the left femur showing marked rickets-like condition.

Fig. 3.—High power photograph of the epiphyseal cartilage—extreme rickets-like lesion showing the arrangement of the cartilage cells in the matrix.

Fig. 4.—Microphotograph of the epiphyseal cartilage from a rat showing a marked rickets-like condition, to show persistence of the cartilage cells and the degenerative changes in them.

Fig. 5.—This picture shows the cell division in cartilage cells which are in contact with tissues of the metaphysis. The cell capsule (c) contains four daughter cells which have arisen by the division of the cartilage corpuscle which originally occupied the capsule.

Fig. 6.—Trabeculæ in the medullary cavity of a rickets-like bone. The small spicule (o) which has undergone calcification is surrounded by a broad zone of osteoid tissue (o. s.).

Fig. 7.—This picture shows the sub-periosteal hyperplasia of the osteoid tissue—the so-called rachitic periostitis.

Fig. 8.—An abortive attempt at healing an extreme rickets-like lesion is recorded in the metaphysis of the affected bone by the linear deposit (l.) of calcium salt.

Fig. 9.—Microphotograph of a bone in which the metaphysis showed traces of three periods of calcium deposition, which are in all cases incomplete or have been partially absorbed.

Fig. 10.—This picture from a section of a bone which was in the transitional stage between the rickets-like condition and osteoporosis shows irregularity and prolongation of the epiphyseal cartilage, and its irregular calcification (cal). Broad zones of osteoid tissue (os) still persist about the trabeculæ.

Fig. 11.—The trabeculæ shown in this figure are further along in the process of absorption than those shown in Fig. 10. Calcification of the cartilage is incomplete in this bone. Osteoid tissue (os) is still present in the diaphysis.

Fig. 12.—Microphotograph showing the cartilage and part of the medullary canal of a bone from a rat maintained on a diet which included a complete salt mixture (185) high in phosphorus. This bone was extremely osteoporotic. The proliferative zone of cartilage (pz) is narrow and was completely and heavily calcified, as was the cortex. There were no trabeculæ in the medullary cavity, and no traces of osteoid tissue to be found in the diaphysis.

GIARDIA (LAMBLIA) INTESTINALIS

A COMMON PROTOZOAN PARASITE OF CHILDREN

By Kenneth F. Maxcy

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Studies of the protozoa found in the intestine of man received a great impetus during the war, due chiefly to the return of large numbers of soldiers from the war area suffering from chronic diarrhœas and dysenteries of various sorts. In investigating the underlying cause of these conditions, a surprisingly high percentage of infestations not only with Entamœba histolytica but also with supposedly non-pathogenic protozoa was disclosed. This led to the examination of non-dysenteric soldiers, of soldiers who had not been outside the country and, finally, of the civilian population in the community at large, with the result that approximately these same percentages were found to hold for all four groups. Pooling the results of all the recent surveys in England, France and the United States, Hegner and Payne[1] find the percentages of infestations with the three commonest intestinal protozoa to be as follows: Entamœba coli 20 per cent, Giardia (Lamblia) intestinalis 12 per cent, and Entamœba histolytica 9 per cent. This work has thrown an entirely different light upon the problem of amœbic dysentery and upon the so-called "flagellate" dysenteries and diarrhœas, of which occasional mention is found in medical literature. It also suggests a reconsideration of the protozoa as intestinal parasites widely distributed in man.

The frequency of Giardia is particularly striking inasmuch as this parasite of man has received little attention in the United States. Although Lambl first described it in 1859, we are really indebted to Grassi for most of our early knowledge concerning the organism. In the early eighties of the last century, he made a careful study of it and demonstrated its habitat to be the upper intestine, where it might be found in huge numbers perched upon the lining epithelium, to which it adhered by means of a sort of sucking disc. He observed a number of individuals who harbored the parasite and thought that in certain instances it was the cause of diarrhœa.

A little later, 1892, Moritz and Hölzl[2] published a lengthy paper on the infestation of man with Giardia, reporting observations on six patients with diarrhœa and upon finding the organism in the duodenum of ten patients dead of tuberculosis. They noted the frequency with which the parasite occurred in children.

Since these early studies, there have appeared in medical literature a large number of reports of the finding of Giardia in the stools of patients, with or without an accompanying diarrhœa. In the United States attention was first called to it by Stiles[3] in 1902, reporting the case of a patient of Dr. Hemmeter of Baltimore, a three-year-old white child with recurring

[1] Hegner, R. W., and Payne, G. C.: Scientific Monthly, 1921, XXI, 47-52.

[2] Moritz and Hölzl: Münch. med. Wchnschr., 1892, XXXIX, 831.

[3] Stiles, C. W.: Washington Medical Annals, 1902, I, 64.

attacks of diarrhœa whose stool contained large numbers of the motile organism. In 1910 Allen [4] reported a similar condition in a five-year-old colored girl. Two years later, in an article by Dubois and Toro,[5] we find an account of four children infested with Giardia.

Emerson,[6] in his text-book, mentions a case discovered in the wards of The Johns Hopkins Hospital. In the Public Health Service Reports of 1911, Stiles [7] makes the statement that Giardia is by no means rare in the United States and says that he encountered it in a number of instances in the course of fecal examinations for parasitic worms in North Carolina. Among 6000 admissions to the Mayo clinic, Giardia was found in 66 or a trifle over 1 per cent,[8] whereas among 1000 admissions to Augustana Hospital in Chicago it was recorded in only five instances, or 0.5 per cent.[9] Finally, in a very careful study of 1500 soldiers of the United States Army, 300 of whom had not been overseas, for intestinal parasites, Kofoid, Kornhauser and Plate [10] report 6 per cent infested with Giardia.

It will be noted that many authors have regarded this organism as pathogenic—that is, as a cause of diarrhœa. This conclusion is usually based upon the presence in the diarrhœic passages of a large number of motile Giardias which apparently disappear with improvement in the clinical condition. In one or two instances examination of tissues removed at operation or after death has seemed to support the contention. In areas where the surface epithelium had been denuded, these protozoa seemed to have penetrated into the wall of the intestine. On the other hand, many have denied it any pathogenic rôle whatsoever, contending that it was present in diseased conditions of the intestine, not as the primary pathogen, but as a secondary invader, that it deserved no more consideration than is given to Entamœba coli, for instance.

Clinical-pathological studies so far published have, then, failed to solve the problem, and attempts have been made to attack it from the experimental side. The method has consisted mainly in inoculating rabbits,[11] guinea-pigs,[12] and rats,[13, 14] with Giardias obtained from man. This method is complicated by the fact that these rodents are in nature infested with their own species of Giardia: Giardia cuniculi in the rabbit, Giardia muris in culture mice and culture rats, and Giardia microti in the meadow mouse, etc. These species are more or less similar in appearance to that found in man and can be distinguished only after careful morphological and biometrical study, and observations on the original habitat. If rodents are to be used in inoculation experiments, natural infestation must be carefully excluded (a feat very difficult of accomplishment), and the origin and classification of the strain of Giardia used in the experiment must have been carefully determined. These and other considerations render previous experimental work on the pathogenicity of Giardia inconclusive. For similar reasons, the statements which have crept into the literature regarding rodents as a reservoir of infection for man have not been firmly established.

To recapitulate, it may be said that previous work has demonstrated that Giardia intestinalis is a widely distributed intestinal parasite of man whose power to harm its host has been strongly suspected but is as yet unproved. Assuming that it is capable of harm, then this should be most apparent at the age when the intestinal tract is most sensitive to disturbing influences of all kinds,—namely, in childhood. The literature lends some support to this hypothesis in so far as many of the cases of so-called "Lamblia enteritis" which have been reported have been in children. The problem formulated is, whether Giardia intestinalis is simply a harmless commensal in children or whether it is capable of causing intestinal disturbance.

As a contribution to the solution of this problem the present study was undertaken to determine the frequency of this parasite in the intestinal tract of apparently normal children in the United States. It is obvious that this information is necessary before its presence in those with abnormal intestinal conditions can be properly evaluated.

Methods and Material

Protozoa are apt to be missed in the ordinary clinical laboratory examination of feces. Specimens are rarely examined immediately after passage, although it is known that the actively motile protozoa die and undergo lysis a few hours after they have left the body of the host. Again, the microscopic examination of feces is often carried out with the low power objective which gives a sufficiently high magnification for the detection of helminth ova; but the detection of the encysted forms of the protozoa require more careful examination, often of several preparations, and with the use of the higher magnifications.

In pursuing the present study, attention was directed toward demonstrating only the encysted Giardia, and incidentally the other common intestinal protozoa which show encysted forms; *viz.*, Entamœba coli, Entamœba histolytica, Endolimax nana, Chilomastix (Tetramitus) mesnili, Coccidia and Blastocystis.

The specimens were obtained for the most part without the previous administration of a cathartic, and were usually formed stools. Two "wet smear" preparations were made from each specimen, distilled water being used. Material for the one was scraped from the exterior of the stool, any clumps of mucus visible being included; material for the second was taken from the interior. A drop of one per cent water soluble eosin was added to the preparation. The field takes a pink stain; the viable cysts remained unstained and stand out rather

[4] Allen, Wm.: Old Dominion Jour. Med. & Surg., 1910, X, 417.
[5] Dubois, E. F., and Wm. C. Toro: Proc. N. Y. Path. Soc., 1912, XII, 32.
[6] Emerson, C. P.: "Clinical Diagnosis," Phila., 2d ed., 1908, pp. 405-406.
[7] Stiles, C. W.: U. S. P. H. S. Reports, 1911, XXVI, 1347.
[8] Logan and Sanford: Jour. Lab. & Clin. Med., 1916-17, II, 618-621.
[9] Smithies, Frank: Am. Jour. Med. Sci., 1918, CLVI, 173.
[10] Kofoid, Kornhauser and Plate: Jour. A. M. A., June, 1919, 72: 1721.
[11] Perroncito: Centralblatt f. Bakt., 1887, II, 738.
[12] Stiles: U. S. P. H. S. Reports, Reprint No. 135, 1913, p. 89.
[13] Fantham and Porter: Brit. Med. Jour., 1916, 2900, II, 139-141.
[14] Yakimoff: Compt. rend. Soc. biol., Paris, 1918, LXXX.

sharply as clearly defined, pale green, refractive ovals against the pink background. Whenever cysts were found to be present, another preparation was made and stained with iodine (iodine 1 part, potassium iodide 2 parts, distilled water 100 parts). This solution differentiates the structures a little more clearly and brings out the iodophilic inclusions.

About 15 minutes were spent in searching through each preparation before it was discarded as negative. An 18 mm. cover-slip was used, and the field was traversed eight times in each direction, guided by a mechanical stage. The "high dry" objective (4 mm.) with a No. 10 B. & L. eye piece gave an approximate magnification of 450 ×.

When possible each patient was examined on two occasions, at intervals of two or more days. Actually the number of examinations averaged two per case. According to Dobell,[15] Wenyon and O'Connor[16] and others, this technique would reveal about two-thirds of the actually existing infestations with intestinal protozoa. This figure probably indicates the percentage of Giardia infestations detected in the present study.

The children examined were miscellaneous medical admissions to the clinic of Dr. John Howland, Harriet Lane Home, Johns Hopkins Hospital. Excepting a small group of "feeding cases," these children were admitted because of acute infectious disease, and were free from gastro-intestinal disturbance. They were fairly representative of the child population of Baltimore with the exception that the negro race was not proportionately represented (only 6 in the 89 were colored).

Results

Of the total of 89 children examined, 18, or 20 per cent, were found to be harboring intestinal protozoa of some type. It is noteworthy that in a group of 15 "feeding cases" under one year of age no infestations were found. The youngest positive case was a little girl 17 months of age whose stools showed large numbers of Entamœba coli cysts. From the second year on there was an increasing number of positive cases with advancing age, so that the group of children from 6 to 12 years old showed a decidedly higher percentage of infestations than the children between one and five.

The relative frequency of the protozoa encountered in this series and the instances of multiple infestations are shown.

Giardia intestinalis (alone)	10 cases
Giardia and Entamœba coli	1
Giardia and Blastocystis	2
Giardia, Hymenolepis nana and Oxyuris vermicularis	1
Entamœba coli (alone)	4
	18

The most interesting fact brought out by this study was the large number of children who harbor Giardia intestinalis. If the infants under one year are excluded, then of the remaining 74 children, 14 were infested with this parasite. In other words one out of every five of the children over one year of age examined harbored Giardia. The raw data indicating the sex and age distribution of these children are given in the accompanying table. The group is in itself too small to admit of conclusive analysis, but may prove of value in connection with other reports of a similar character in the literature.

TABLE 1.—AGE AND SEX DISTRIBUTION OF CHILDREN FOUND TO BE INFESTED WITH GIARDIA (LAMBLIA) INTESTINALIS

Age	Males 58		Females 31		Total 89	
	Non-infested 52	Infested 6	Non-infested 23	Infested 8	Non-infested 75	Infested 14
0— 1	12	0	3	0	15	0
1— 2	10	0	4	1	14	1
2— 3	6	1	5	0	11	1
3— 4	9	0	2	1	11	1
4— 5	3	2	1	2	6	4
5— 6	2	0	3	1	5	1
6— 7	2	0	1	1	3	1
7— 8	0	2	1	1	1	3
8— 9	1	0	0	1	1	1
9—10	1	0	1	0	2	0
10—11	1	0	0	0	1	0
11—12	1	1	2	0	3	1
12—13	2	0	0	0	2	0

The youngest instance of Giardia infestation was in a little girl 22 months old. In the group of one to five years of age, 17 per cent showed Giardia, and from 6 to 12 almost 40 per cent were positive.

The history of each one of these positive cases was obtained. None had suffered from chronic diarrhœa so far as could be learned. One gave a history of a rather severe diarrhœa in the preceding summer, but such a history might be expected in at least one of a group of this size, and no conclusions as to its etiology could be drawn. Three of the children showed a tendency toward increased frequency of defecation—three or four times daily. This may be a significant observation, as it is what one might expect from duodenal irritation.

Case 38, a child five years old, had on admission a diarrhœa. The passages were dark brown in color and contained a large amount of yellowish mucus in which were entangled myriads of motile Giardia. The condition, however, cleared quickly and after two or three days only the encysted forms could be found in the soft, semi-formed stools, which, however, still contained some mucus at times. No history of repeated attacks of diarrhœa was obtainable in this individual.

The intermittency with which Giardia cysts are discharged was particularly well illustrated by two of the series. In case 19, examinations on January 27, 29 and 31 were negative; on February 3 and 5 large numbers of Giardia were found. In Case 37, the examination on February 24 was positive. No cysts were found on February 27, 29 and March 4. On March 6 large numbers of cysts were again found and were still present at the last examination on March 11.

[15] Medical Research Committee, National Health Insurance, London. 1918, Special Report Series Nos. 7 and 15; 1921, No. 59.

[16] Wenyon and O'Connor, J.: Royal Army Med. Corps, 1917, XXVIII, 1-24.

DISCUSSION

This intermittency emphasizes the necessity of repeated examinations for the establishment of a negative result, in order to judge of the heaviness of the infestation or the permanency of a cure. This has been pointed out by many observers. An attempt has been made to show that Giardia undergoes a regular cycle of cyst production. Porter [17] made daily examinations of a group of soldiers infested with Giardia and estimated the number of cysts passed in 24 hours. The number varied within wide limits, being practically nil on some days and more than 300,000 on other days. She estimated the interval between successive maxima and minima at about 14 days. Boeck,[18] working with the Giardia microti of the meadow mouse, found a similar phenomenon but fixed the interval at seven days. Dobell,[19] on the other hand, finds absolute irregularity in the passage of cysts, suggesting that there may be prolonged periods of complete quiescence during which no cysts can be found.

At all events, it is plainly evident that a single examination or two examinations reveals only a part of those actually parasitized. In the series here reported, while Giardia was actually found in one out of every five children examined, a conservative estimate would place those actually infested at close to one in four.

Results of British investigations [20] indicate a similar high degree of incidence of Giardia in the intestinal tract of children in that country. Matthews and Smith examined 548 children in the Liverpool Royal Infirmary, and, based upon a single examination per case, found 14 per cent infested with this protozoon. A. H. Campbell found 16 per cent positive in a group of 49 children under 12 years of age in the Children's Hospital, St. Michael's Hill, Bristol.

Muriel M. Nutt examined 128 children in Leeds, England. Among a group of children living in an institution (Workhouse), 48.8 per cent were found to harbor Giardia as compared with 23.9 per cent of the children in the Leeds General Infirmary. The higher incidence among inmates of an institution is a significant fact. In the Sheffield Royal Hospital, this same observer found 15.8 per cent of 57 children examined positive for Giardia.

Most of these figures are based upon a single examination per case. It seems to be clearly established that in England Giardia is a very common intestinal protozoon in children. Our own studies indicate that the same thing is true in the United States.

How soon the infestation is acquired is a question of considerable interest and importance. It has been noted that no cases were found among the 15 infants under one year of age examined. Matthews and Smith found none among the 50 infants which were examined by them. On the other hand, Miss Nutt found no less than 6 of the 25 children under 12 months of age examined by her to be harboring Giardia. The ages were respectively: one at three weeks, one at three months, one at nine months, one at eleven months and two at twelve months. That an infant three weeks old may become infested with Giardia is a startling fact, and indicates how soon the food of children in filthy surroundings becomes contaminated with human fecal material. However, this must certainly be an exceptional case, and infestation during the first year of life is a comparatively rare event.

Sufficient figures are not yet at hand to determine at what year of childhood the maximal incidence is found, but it is not unlikely that it is before the fifth year as is the case with Oxyuris vermicularis. Indeed, these two parasites may be transmitted from child to child in much the same way. Experimental work has demonstrated that Giardia cysts can remain alive outside the human host for only a few hours except under very favorable circumstances as regards moisture and absence of other deleterious influences. If allowed to dry, they perish immediately. An intermediate host has not been shown to exist nor to be necessary. The obvious inference on the basis of our present knowledge is a rather direct transference by fecal contamination of fingers and food. Without doubt it is just one more of the unwelcome guests along with the tubercle bacillus and metazoan parasites which children pick up during the "dirty age."

How long the infestation may last is as yet undetermined. This much is certain: A very much higher incidence is detected in children than in adults. The British figures are very consistent on this point. In the same population groups, the percentage of adults showing Giardia cysts is from one-third to one-fifth that of the children. In this country, as previously mentioned, Kofoid, Kornhauser and Plate found 6 per cent of the healthy, young adult soldiers who had never been outside the United States harboring Giardia. If this figure is compared with the 20 per cent of children found infested in this investigation, the same discrepancy is apparent.

The explanation suggested is that in a certain number of children the infestation is not permanent, and that there is either a heightened immunity or lessened exposure in adult life. The same phenomenon has been noted in the protozoon infestations of certain animals, namely, that the young of the species show a far greater degree of infestation than the adults of the same species. Here the lessened exposure is not so obvious and greater emphasis must be laid upon factors of immunity. These latter may simply be changes in the bacterial flora of the intestine or in food habits. To these views Dobell [19] objects that it has not yet been demonstrated in any particular instance that an individual once infested with Giardia has subsequently been ridded of the parasite. Absence of the cysts in the stools does not necessarily mean that the organism is no longer present in the intestinal tract. Cyst production may be in abeyance in adults. He has himself observed an infected individual over ten years, and although it is

[17] Porter, Annie: Lancet, London, 1916, I, 1166-69.
[18] Boeck, Wm. C.: Univ. of Cal. Pub., Berkeley, 1919, XIX, 85.
[19] Dobell, Clifford: Lancet, London, 1916, II, 1053.
[20] Medical Research Council, London, 1921, Special Report Series, No 59.

frequently impossible to find the organism in the stools the infection is still present and has shown no disappearance from the bowel. Obviously it is just as wrong to generalize from this one case, and until it has been proved that Giardia is as frequent in the intestinal tract of adults as in children, it may be assumed that a certain number of children do get rid of their Giardia infestations.

As regards the pathogenicity of Giardia, in view of the large number of apparently normal children harboring the organism the conclusion is almost forced that in a vast majority of instances it is present merely as a harmless commensal. On the other hand, the fact that, in at least one of the 14 positive cases found in this investigation, there was evidence of an intestinal disturbance which could possibly be attributed to Giardia makes necessary guarded inferences as to its entire harmlessness in children—particularly in very young children.

There seem to be authentic instances in the literature in which individuals harboring this parasite have been subject to recurrent attacks of diarrhœa, during which they passed large quantities of yellowish mucus in which occur the unencysted Giardia in myriads, and in whom no other explanation for the diarrhœa is obvious. As Wenyon and O'Connor [a] point out, it is difficult to explain the large quantity of mucus or the occasion of the attacks and, above all, the crowding of the mucus with flagellates, without assuming that the mucus must be produced by the intestine at the site of the Giardia infection and that the flagellates are directly responsible for its production.

Before this parasite is ruled out as of no importance to children, a larger experience is required. Its presence or absence should be recorded in a large series of children suffering from nutritional difficulty, intestinal "indigestion," abnormal frequency of defecation, diarrhœa, etc., and compared with a like group of children, normal in these respects, and living under the same surroundings.

On the basis of this recent knowledge it is evident that the mere finding of a considerable number of Giardia in the stools of a child suffering with diarrhœa and dysentery does not necessarily mean that Giardia is the cause of the condition. In fact it would be strange if a great many such cases were not found. Misdirected efforts at therapy should also be avoided. There is no evidence at the present time that any of the innumerable drugs that have been used are of the slightest value in ridding the patient permanently of his infestation.

Conclusions

1. Giardia intestinalis is present in the intestinal tract of a large percentage of apparently normal children.
2. It is rarely found before the first year.
3. The percentage of infestations appears to be much higher in childhood than in adult life.
4. The finding of a large number of motile Giardia in a diarrhœa or dysenteric stool is not sufficient evidence to establish the etiologic relationship of this parasite.
5. In certain rare instances the parasite may be responsible for some intestinal disturbance, although this point has not yet been firmly established.

[a] Wenyon and O'Connor: "Human Intestinal Protozoa in the Near East," Wellcome Bureau of Scientific Research, London, 1917.

NOTES ON NEW BOOKS

The Form and Functions of the Central Nervous System. An Introduction to the Study of Nervous Diseases. By Frederick Tilney, M.D., and Henry A. Riley, M.D. Cloth, $12.00. (*New York, Paul B. Hoeber, 1921.*)

In one volume of a thousand pages the authors have combined the important data which are indispensable to a proper understanding of clinical neurology. No laborious attempt to correlate a mass of anatomical facts by doubtful significance has been made. The importance of phylogenetic investigations in relation to the functions of the nervous system of man has been clearly stated.

The work is of particular value to students and clinicians, since it contains much information not available in text-book form in English. Furthermore, that information is clearly set forth in a rational manner. The microphotographs and drawings are in most instances well reproduced. A few of the former are so dark that detail is lost. Very few authors are cited in the text, but a fairly complete bibliography is appended.

The field of usefulness for the book exists and its appearance should be welcomed. V. R. M.

Physiology and Pathology of the Cerebrospinal Fluid. By William Boyd. Cloth. (*New York: MacMillan Co., 1920.*)

In his preface the author states that "the object of this book is to present some of the fascinating physiological problems connected with the cerebrospinal fluid, and to show how they are related to the pathological problems which more directly concern the clinician." This object is attained. The subject is presented from a physiological standpoint in a clear, if somewhat elementary, fashion. The more recently discovered facts pertaining to the origin and circulation of the cerebrospinal fluid, and the finer anatomical relationships of the subarachnoid space are brought together and correlated in Part I.

Part II of the book deals with the cerebrospinal fluid in special pathological conditions, and a section on therapeutics is herein included. It is to be regretted that Part I was not elaborated in more detail—to the complete exclusion of Part II from the volume. An excellent bibliography is given. H. M.

The Mechanism and Graphic Registration of the Heart Beat. By Thomas Lewis, M.D. Cloth, $16.00. (*New York: Paul B. Hoeber, 1920.*)

Although advance in special methods of cardiac study has been remarkably rapid in the last few years, one cannot but feel that in a way the crest of the wave has been reached. General principles have been pretty well established, and it now remains mainly to work out the finer details of the disturbances of cardiac mechanism. Another edition of Lewis's masterly treatise seems, therefore, most timely, bringing up to date, as it does, the whole subject. As those familiar with the previous editions know, the subject is taken up mainly from the standpoint of pathological physiology. The authority of the writer and the constant references to his own work do not interfere with a critical discussion of the literature in general, so that the book stands out as a storehouse of information in this large and complex domain of medical science. A. L. B.

BOOKS RECEIVED

Scurvy, Past and Present. By Alfred Hess, M.D. Illustrated. 1920. 8°. 279 pages. J. B. Lippincott Company, Philadelphia and London.

A Handbook of Midwifery. For Midwives, Maternity Nurses, and Obstetric Dressers. By Comyns Berkeley, M. A., M. C., M. D. (Cantab.), F. R. C. P., Lond., M. R. C. S., Eng. Fifth edition, enlarged with color frontispiece and 74 illustrations in the text. 1921. 16°. 550 pages. Paul B. Hoeber, New York.

Insects and Human Welfare. An Account of the More Important Relations of Insects to the Health of Man, to Agriculture, and to Forestry. By Charles Thomas Brues. 1920. 8°. 104 pages. Harvard University Press, Cambridge.

The Basis of Psychiatry (Psychobiological Medicine). A Guide to the Study of Mental Disorders for Students and Practitioners. By Albert C. Buckley, M. D. 79 illustrations. 1920. 8°. 447 pages. J. B. Lippincott Company, Philadelphia and London.

Old at Forty or Young at Sixty. Simplifying the Science of Growing Old. By Robert S. Carroll, M. D. 1920. 12°. 147 pages. Macmillan Company, New York.

Surgery of the Lung and Pleura. By H. Morriston Davies, M. A., M. D., M. C. (Cantab.), F. R. C. S. (Eng.), Hon. Captain R. A. M. C. (T.). 1920. 8°. 259 pages. Paul B. Hoeber, New York.

French-English Medical Dictionary. By Alfred Gordon, A. M., M. D. (Paris). 1921. 8°. 161 pages. P. Blakiston's Son & Co., Philadelphia.

La Question des Vitamines. Par le Docteur G. Houlbert. 1921. 12°. 91 pages. Louis Arnette, Paris.

Nucleic Acids. Their Chemical Properties and Physiological Conduct. By Walter Jones, Ph. D. Second Edition. 1920. 8°. 150 pages. Longmans, Green and Co., London.

Annals of Roentgenology. A Series of Monographic Atlases. Edited by James T. Case, M. D. *Mastoids Roentgenologically Considered.* By Frederick M. Law, M. D. Volume I. 1920. 4°. 39 pages. Paul B. Hoeber, New York.

Hygiene of Communicable Diseases. A Handbook for Sanitarians, Medical Officers of the Army and Navy and General Practitioners. By Francis M. Munson, M. D. 1920. 12°. 793 pages. Paul B. Hoeber, New York.

Nurses Handbook of Drugs and Solutions. By Julia C. Stimson, R. N. Third Edition. 1920. 12°. 113 pages. Whitcomb & Barrows, Boston.

Oxford Medical Publications. Publishers: Henry Frowde, London; Hodder & Stoughton, London. The following four volumes.

Tropical Ophthalmology. By Robert Henry Elliot, M. D., B. S. (Lond.), Sc. D. (Edin.), F. R. C. S. (Eng.). With 7 plates and 117 illustrations. 1920. 8°. 525 pages.

A Text Book of Pharmacology and Medical Treatment for Nurses. By J. M. Fortescue-Brickdale, M. A. (Oxon.), M. R. C. P. (Lond.), Capt. R. A. M. C. (T. F.). 1920. 8°. 392 pages.

Common Infections of the Kidneys with the Colon Bacillus and Allied Bacteria. Based on a Course of Lectures Delivered at the London Hospital. By Frank Kidd, M. B., B. C. (Cantab.), F. R. C. S. (Eng.). With an additional lecture on the *Bacteriology of the Urine.* By Dr. Philip Panton. 1920. 8°. 331 pages.

Clinical Ophthalmology. For the General Practitioner. By A. Maitland Ramsay, M. D. With foreword by Sir James Mackenzie, M. D., F. R. S. 1920. 8°. 500 pages.

History and Bibliography of Anatomic Illustrations in its Relation to Anatomic Science and the Graphic Arts. By Ludwig Choulant. Translated and edited with notes and a biography. By Mortimer Frank, B. S., M. D. With a biographical sketch of the translator and two additional sections. By Fielding H. Garrison, M. D., and Edward C. Streeter, M. D. 1920. 8°. 435 pages. The University of Chicago Press, Chicago, Illinois.

The Form and Functions of the Central Nervous System. An Introduction to the Study of Nervous Diseases. By Frederick Tilney, M. D., Ph. D., and Henry Alsop Riley, A. M., M. D. Foreword by George S. Huntington, Sc. D., M. D. 591 figures containing 763 illustrations of which 56 are colored. 1921. 4°. 1020 pages. Paul B. Hoeber, New York.

Nouveau Traité de Médecine. Par G. H. Roger, Fernand Widal, et P. J. Teissier, Secrétaire de la Rédaction: M. Garnier. Fascicule premier, *Maladies Infectieuses.* 1920. 8°. 482 pages. Masson et Cie, Paris.

Hookworm and Malaria Research in Malaya, Java, and the Fiji Islands. Report of Uncinariasis Commission to the Orient 1915-1917. S. T. Darling, M. D., M. A. Barber, Ph. D., H. P. Hacker, M. D. Publication No. 9. 1920. 8°. 191 pages. The Rockefeller Foundation, International Health Board, New York City.

United States Navy Department Bureau of Medicine and Surgery. Annual Report of the Surgeon General, U. S. Navy, to the Secretary of the Navy for the Fiscal Year 1920. 8°. 326 pages. Government Printing Office, Washington.

PUBLICATIONS

The following twelve monographs:

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price, 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, $2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D. Price, 75 cents.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, $2.00.

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